(FILE 'CAPLUS' ENTERED AT 12:12:53 ON 29 JUN 2001)
L1 58 SEA FILE=CAPLUS ABB=ON PLU=ON (AD(S)ADENOVIR? OR ADENOVIR? OR ADENO VIR?) AND VIRAL CAPSID
L2 9 SEA FILE=CAPLUS ABB=ON PLU=ON L1 AND LIGAND

L2 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:338691 CAPLUS
DOCUMENT NUMBER: 134:348931
TITLE: Use of reversibly immobilized complex forming proteins in the packaging of molecules in protein shells
INVENTOR(S): Boehm, Gerald; Esser, Dirk; Schmidt, Ulrich
PATENT ASSIGNEE(S): Acgt Progenomics A.-G., Germany
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032852	A2	20010510	WO 2000-EP10878	20001103
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19952982	A1	20010517	DE 1999-19952982	19991103

PRIORITY APPLN. INFO.: DE 1999-19952982 A 19991103

AB The invention relates to a method for packaging mol. substances in protein shells. A component of the protein shell is immobilized on a suitable matrix. The immobilized protein is incubated with the substance of interest to allow binding of the two mols. The protein shell fragment with the bound mol. is then released from the matrix. The shell fragments carrying the mol. is incubated with other protein shell fragments to form a protein shell, whereby the sepn. and assembly can be carried out in any order. The method can be used to encapsulate nucleic acids in **viral capsids** in vitro without the need for packaging cell lines. The capsid proteins may be further modified by inclusion of affinity **ligands** for cell surface receptors. Use of variants of

polyomavirus VP1 protein to encapsulate a plasmid is demonstrated. Specifically, a fusion protein of VP1, an intein, and a chitin binding domain was constructed and immobilized on a chitin surface. After immobilization, the capsid protein could be released by treatment with dithiothreitol and hydroxylamine.

L2 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:338690 CAPLUS
DOCUMENT NUMBER: 134:348930
TITLE: Modular systems based on **viral capsids** for the construction of delivery vehicles for gene therapy
INVENTOR(S): Boehm, Gerald; Rudolph, Rainer; Schmidt, Ulrich; Esser, Dirk
PATENT ASSIGNEE(S): ACGT Progenomics A.-G., Germany
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032851	A2	20010510	WO 2000-EP10876	20001103
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19952957	A1	20010517	DE 1999-19952957	19991103

PRIORITY APPLN. INFO.: DE 1999-19952957 A 19991103

AB A method of delivering nucleic acids to target cells in modified **viral capsids** is described. The method uses **viral capsids** assembled from a combination of modified and unmodified capsid proteins to enclose the nucleic acids upon in vitro assembly. The modified capsid proteins may contain an affinity **ligand** to target a specific cell type. The construction of a no. of amino acid substitution variants of the VP1 capsomere protein of polyomavirus is described. Selective substitution of cysteine residues with serine to alter intra- and inter-disulfide bonding is demonstrated. Proteins carrying an RGD

peptide or with diminished ability to bind sialyllactose are described. The ability of different populations of VP1 carrying different labels to form mixed capsids is demonstrated. These mixed capsids could be used to infect animals cells in culture.

L2 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:95807 CAPLUS
TITLE: Influence of **adenoviral** fiber mutations on viral encapsidation, infectivity and in vivo tropism
AUTHOR(S): Leissner, P.; Legrand, V.; Schlesinger, Y.; Hadji, D. A.; Van Raaij, M.; Cusack, S.; Pavirani, A.; Mehtali, M.
CORPORATE SOURCE: Transgene SA, Strasbourg, 67000, Fr.
SOURCE: Gene Ther. (2001), 8(1), 49-57
CODEN: GETHEC; ISSN: 0969-7128
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Targeting of **adenovirus** (**Ad**)-encoded therapeutic genes to specific cell types has become a major goal in gene therapy. Redirecting the specificity of infection requires the abrogation of the natural interaction between the viral fiber and its cellular receptors (CAR) and the simultaneous introduction of a new binding specificity into the **viral capsid**. To abrogate the natural affinity of the fiber, we have mutated residues presumed to be directly or indirectly involved in CAR-binding in the knob domain of the fiber protein. These residues are located in the AB loop (Ser408) and in the DG loop (Tyr491, Ala494, Ala503). The mutations Ser408Glu, Tyr491Asp, Ala494Asp and Ala503Asp did not prevent the incorporation of trimeric fibers in the **viral capsid** but led to loss of CAR binding in vitro. Infectivity of the mutant viruses could be restored in vitro by introducing a **ligand** at the C-terminal end of the knob, confirming that the reduced infectivity of the fiber-modified virus was due to an impaired interaction of the viral particle with the CAR receptor. However, after systemic delivery, the in vivo biodistribution of impaired CAR-binding viruses without addn. of a specific **ligand** was not altered when compared with wild-type Ad.

REFERENCE COUNT: 49
REFERENCE(S):
(1) Becker, K; Hum Gene Ther 1999, V10, P2559 CAPLUS
(2) Bergelson, J; Science 1997, V275, P1320 CAPLUS
(3) Bewley, M; Science 1999, V286, P1579 CAPLUS
(4) Bouri, K; Hum Gene Ther 1999, V10, P1633 CAPLUS

(5) Bramson, J; Curr Opin Biotech 1995, V6, P590
CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:846228 CAPLUS
DOCUMENT NUMBER: 134:361965
TITLE: Recombinant **adenovirus** vectors with knobless fibers for targeted gene transfer
AUTHOR(S): Van Beusechem, V. W.; Van Rijswijk, A. L. C. T.; Van Es, H. H. G.; Haisma, H. J.; Pinedo, H. M.; Gerritsen, W. R.
CORPORATE SOURCE: Division of Gene Therapy, Department of Medical Oncology, University Hospital Vrije Universiteit, Amsterdam, 1007 MB, Neth.
SOURCE: Gene Ther. (2000), 7(22), 1940-1946
CODEN: GETHEC; ISSN: 0969-7128
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Adenoviral** vector systems for gene therapy can be much improved by targeting vectors to specific cell types. This requires both the complete ablation of native **adenovirus** tropism and the introduction of a novel binding affinity in the **viral capsid**. We reasoned that these requirements could be fulfilled by deleting the entire knob domain of the **adenovirus** fiber protein and replacing it with two distinct moieties that provide a trimerization function for the knobless fiber and specific binding to the target cell, resp. To test this concept, we constructed **adenoviral** vectors carrying knobless fibers comprising the .alpha.-helix trimerization domain from MoMuLV envelope glycoprotein. Two mimic targeting **ligands**, a Myc-epitope and a 6His-tag, were attached via a flexible linker peptide. The targeted knobless fiber mols. were properly expressed and imported into the nucleus of **adenovirus** packaging cells, where they were incorporated as functional trimers into the **adenovirus** capsid. Both **ligands** were exposed on the surface of the virion and were available for specific binding to their target mols. Moreover, the knobless fibers mediated gene delivery into cells displaying receptors for the coupled **ligand**. Hence, these knobless fibers are prototype substrates for versatile addn. of targeting **ligands** to generate truly targeted **adenoviruses**.
REFERENCE COUNT: 33
REFERENCE(S): (1) Chan, S; Mol Cell Probes 1987, V1, P73 CAPLUS
(2) Cohen, C; Proteins Structure Function, Genetics 1990, V7, P1 CAPLUS

(3) Dmitriev, I; J Virol 1998, V72, P9706 CAPLUS
(4) Douglas, J; Nat Biotechnol 1996, V14, P1574 CAPLUS
(5) Douglas, J; Nat Biotechnol 1999, V17, P470 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:787046 CAPLUS
TITLE: Biophysical targeting of **adenovirus** vectors for gene therapy
AUTHOR(S): Silman, Nigel J.; Fooks, Anthony R.
CORPORATE SOURCE: Centre for Applied Microbiology and Research, Salisbury, SP4 0JG, UK
SOURCE: Curr. Opin. Mol. Ther. (2000), 2(5), 524-531
CODEN: CUOTFO; ISSN: 1464-8431
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

What month was this published?

AB Advances in understanding the interaction of animal viruses with their cognate receptors has led to improvements in the development of cell-specific, targeted viral vectors. Research strategies to generate safe, non-inflammatory viral vectors that are capable of delivering a therapeutic gene to a specific population of cells are currently underway in many labs. One approach in the utilization of this cell targeting activity is to ablate the natural interaction of the virus with its native receptor, although this is not an abs. requirement. The initial development of "viral targeting strategies" was based on the view that by modifying the viral protein/receptor interaction, it would be possible to redirect virus vectors to new host cells. As the understanding of virus/cell interactions increased it was obsd., however, that many viruses can use different entry mechanisms for cell attachment and penetration. **Adenovirus** vectors have been used extensively for the delivery of genes to cells. The entry mechanism for **adenoviruses** into cells has recently been studied and is relatively well understood, however, there are many aspects of cell receptor/virus interactions, which have still to be elucidated. The single high-affinity receptor on mammalian cells for **adenovirus** type 5 is recognized as the coxsackie and **adenovirus** receptor. However, in the absence of coxsackie and **adenovirus** receptor other receptors are used. A thorough understanding of the biol. of **adenoviruses** is essential in the further development of their use as vectors for cell targeting. One strategy is to modify the **viral capsid**, either through coating the surface using bispecific antibodies, or by chem. crosslinking the targeting **ligand** onto the virion surface. Another approach is to genetically modify

the virus by incorporating the targeting **ligand** into the viral "spike" (fiber) protein. This involves manipulating the **adenovirus** genome and generating a new targeting **ligand** on the surface of the fiber protein using recombinant DNA technol. The penton base protein has also received attention as a means of directing **adenoviruses** via insertion of novel targeting **ligands**.

REFERENCE COUNT: 70
REFERENCE(S):
(1) Amalfitano, A; Gene Ther 1999, V6, P1643 CAPLUS
(2) Baker, A; Gene Ther 1997, V4, P773 CAPLUS
(3) Bergelson, J; Science 1997, V275, P1320 CAPLUS
(4) Bouri, K; Hum Gene Ther 1999, V10, P1633 CAPLUS
(5) Clesham, G; Gene Ther 1998, V5, P174 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:761432 CAPLUS
DOCUMENT NUMBER: 132:938
TITLE: Methods for prolonging the expression of a heterologous gene of interest in viral vectors using soluble CTLA4 molecules and an antiCD40 **ligand**
INVENTOR(S): Linsley, Peter S.; Kay, Mark A.; Wilson, Christopher B.; Ledbetter, Jeffrey; Aruffo, Alejandro A.; Hollenbaugh, Diane L.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: U.S., 21 pp., Cont.-in-part of U.S. Ser. No. 468,407, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5993800	A	19991130	US 1995-474210	19950606
WO 9639514	A1	19961212	WO 1996-US8974	19960605
W: CA, JP, MX				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2223412	AA	19961212	CA 1996-2223412	19960605
EP 832227	A1	19980401	EP 1996-919102	19960605
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

JP 11510685 T2 19990921 JP 1996-501407 19960605
PRIORITY APPLN. INFO.: US 1995-468407 19950605
US 1995-474210 19950606
WO 1996-US8974 19960605

AB The invention provides a method for enhancing the expression of a gene of interest by a cell, the cell (a) comprises a recombinant nucleic acid sequence encoding and (b) is capable of expressing the gene of interest, the method comprising contacting the cell with an amt. of a sol. CTLA4 mol. effective to enhance the expression of the gene of interest by the cell. This gene of interest is part of a recombinant viral vector that is stably incorporated into a target cell. This has applications in gene therapy and immunotherapy as CTLA4 is a cell surface antigen normally found on T cells. It binds to the B cell activation antigen B7. A sol. CTLA4 mol. has been shown to inhibit immune responses dependent on the interaction between T and B cells. Blunted humoral immunity against an **adenovirus** vector was achieved where prodn. of neutralizing antibodies was reduced. It involves administering to the subject an amt. of a sol. CTLA4 effective to enhance the amt. or duration of expression of a gene capable of inhibiting the disease or assocd. symptoms.

REFERENCE COUNT: 28
REFERENCE(S): (1) Adam; J Virol 1988, V62, P3802 CAPLUS
(2) Algate; Blood 1994, V83(9), P2459 CAPLUS
(3) Anderson; US 5399346 1995 CAPLUS
(4) Anon; EP 0613944 1994 CAPLUS
(6) Armentano; J Virol 1987, V61, P1647 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:759764 CAPLUS
DOCUMENT NUMBER: 130:112400
TITLE: Successful readministration of adeno-associated virus vectors to the mouse lung requires transient immunosuppression during the initial exposure
AUTHOR(S): Halbert, Christine L.; Standaert, Thomas A.; Wilson, Christopher B.; Miller, A. Dusty
CORPORATE SOURCE: Fred Hutchinson Cancer Research Center, Seattle, WA, 98109, USA
SOURCE: J. Virol. (1998), 72(12), 9795-9805
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The airway is an important target for gene transfer to treat cystic fibrosis and other diseases that affect the lung. We previously found that marker gene expression did not persist in the bronchial

epithelium following adeno-assocd. virus (AAV) vector administration to the rabbit lung. In an attempt to promote continued expression, we tested repeat vector administration, but no addnl. transduction was obsd., and the block to transduction correlated with the appearance of neutralizing antibodies to the **viral capsid**. Here we show that mice exhibit a similar response but that treatment with anti-CD40 **ligand** antibody (MR1) and a sol. CTLA4-Ig fusion protein (CTLA4Ig) at the time of primary AAV vector exposure allowed successful repeat transduction and prevented prodn. of neutralizing antibodies. We also tested the possibility that an immune response caused the loss of marker-pos. cells in the epithelial population in rabbits by evaluating AAV vector expression in immunocompetent and immunodeficient mice. In contrast to results in rabbits, marker protein expression persisted in the lung in both groups of mice. AAV vector transduction occurred in alveolar cells, airway epithelial cells, and smooth muscle cells, and vector expression persisted for at least 8 mo. Although data on persistence of AAV vector expression in the human lung are not available, it is likely that repeat transduction will be necessary either due to loss of expression or to the need for repeat administration to deliver effective amts. of AAV vectors. Results presented here indicate that transient immunosuppression will allow such repeat vector treatment of the lung.

REFERENCE COUNT: 38

REFERENCE(S):
(1) Alexander, I; Hum Gene Ther 1996, V7, P841 CAPLUS
(2) Allen, J; J Virol 1997, V71, P6816 CAPLUS
(5) Bierer, B; Proc Assoc Am Physicians 1995, V107, P28 CAPLUS
(6) Bluestone, J; Immunity 1995, V2, P555 CAPLUS
(7) Boissy, R; Gene 1985, V35, P179 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:621330 CAPLUS
DOCUMENT NUMBER: 129:240871

TITLE: **Adenoviral** vectors with modified tropism for gene therapy

INVENTOR(S): Sosnowski, Barbara A.; Baird, Andrew; Pierce, Glenn F.; Curiel, David T.; Douglas, Joanne T.; Rogers, Buck E.
PATENT ASSIGNEE(S): USA

SOURCE: PCT Int. Appl., 205 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9840508	A1	19980917	WO 1998-US4964	19980313
W: AL, AM, AT, AU, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9864629	A1	19980929	AU 1998-64629	19980313
EP 973926	A1	20000126	EP 1998-910375	19980313
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.:		
	US 1997-40782	19970314
	US 1997-65265	19971110
	WO 1998-US4964	19980313

AB The present invention relates to gene therapy. In particular, therapeutic agents, therapeutic gene products, and compns. are disclosed. Various systems and methods useful in targeting and delivering non-native nucleotide sequences to specific cells are disclosed, wherein virus-antibody-**ligand** conjugates are used to facilitate targeting and delivery. Thus, FAB-fibroblast growth factor 2 conjugates are constructed by linking modified recombinant fibroblast growth factor (FGF) with the FAB fragment from a blocking monoclonal antibody, 1D6.14, which was generated against **adenovirus** type 5 knob region. FGF2 retargeting of an **adenovirus** (i.e., altering the tropism of an **adenovirus** using a fibroblast growth factor) significant enhances targeting efficiency and nuclear trafficking of the **adenovirus** vector well above that seen when the vector retains its native **adenoviral** tropism. In addn., FGF retargeting increases the infectability of **adenovirus** in various cells (e.g., cells expressing Kaposi's sarcoma) compared to the use of native **adenovirus** tropism alone, even in cell lines hat are resistant to **adenovirus** infection. The use of FGF retargeting vectors enhances potency; FGF-retargeted vectors deliver and promote the expression of a therapeutic gene to more target cells and in each cell so targeted. The vectors of the present invention are also significantly less toxic to the liver and are less immunogenic than are other **adenovirus** vectors. Finally, retargeting the viral vector retarged with FGF induces cytotoxicity to specific cell types when therapeutic gene sequences (e.g., cytotoxic sequences, such as herpes simplex virus thymidine kinase) are delivered. FGF retargeted vectors are thus able to

transduce cells which are normally insensitive to **adenovirus** infection.

L2 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:174642 CAPLUS
DOCUMENT NUMBER: 128:307304
TITLE: Transient immunosuppression allows transgene expression following readministration of adeno-associated viral vectors
AUTHOR(S): Manning, William C.; Zhou, Shangzhen; Bland, Mary Pat; Escobedo, Jaime A.; Dwarki, Varavani
CORPORATE SOURCE: Chiron Corporation, Emeryville, CA, 94608, USA
SOURCE: Hum. Gene Ther. (1998), 9(4), 477-485
CODEN: HGTHE3; ISSN: 1043-0342
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Adeno-assocd. viral (AAV) vectors have much promise in gene therapy. Among the many properties that make AAV an ideal vector for gene therapy are its ability to infect both dividing and nondividing cells and the longevity of expression in tissues such as brain, skeletal muscle, and liver. However, like other viral vectors, readministration of vector is limited because of the host's immune response to viral components of the vector. Using class I, class II, and CD40 **ligand** (CD40L)-deficient mice, the authors demonstrate that neutralizing antibodies to the **viral capsid** proteins prevent transgene expression following readministration of rAAV vectors. Transient immunosuppression of mice by treatment with antibody to CD4 at the time of primary infection allowed transgene expression after readministration of rAAV vectors to animals. Transient immunosuppression with antibody to CD40L had only a modest effect on the efficacy of readministration. The ability to readminister virus was inversely correlated with both AAV capsid ELISA titers and AAV neutralizing antibody titers. Thus, readministration of rAAV can be accomplished by down regulating the anti-AAV immune response and the use of repeated administration of rAAV is suggested as a viable form of therapy for the treatment of chronic diseases.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 12:17:58 ON 29 JUN 2001)
L3 19 S L2
L4 7 DUP REM L3 (12 DUPLICATES REMOVED)

L4 ANSWER 1 OF 7 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001224005 MEDLINE
DOCUMENT NUMBER: 21114191 PubMed ID: 11162317
TITLE: Uptake of **adenoviral** vectors via fibroblast

Searcher : Shears 308-4994

growth factor receptors involves intracellular pathways that differ from the targeting **ligand**.

AUTHOR: Hoganson D K; Sosnowski B A; Pierce G F; Doukas J
CORPORATE SOURCE: Selective Genetics, Inc., 11035 Roselle Street, San Diego, California 92121, USA..
hoganson@selectivegenetics.com

CONTRACT NUMBER: R43CA79294 (NCI)
SOURCE: MOLECULAR THERAPY, (2001 Jan) 3 (1) 105-12.
Journal code: DRT; 100890581. ISSN: 1525-0016.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010502
Last Updated on STN: 20010502
Entered PubMed: 20010222
Entered Medline: 20010426

AB Target-specific delivery of **adenoviral** gene therapy vectors has been achieved by introducing basic fibroblast growth factor (FGF2) onto **viral capsids**. FGF2-retargeted vectors enter the cell through high-affinity FGF receptors while normal **adenoviral** receptor interactions are ablated. In addition, FGF2-mediated targeting permits a higher level of transgene expression and in vivo efficacy. We now present studies on the intracellular pathways and mechanisms of transduction by FGF2-retargeted **adenovirus**. FGF2 retargeting results in increased virion entry. Nuclear delivery is also increased, but to a level that is directly proportional to virion entry. In addition, after entry, the retargeted particle rapidly localizes to the nucleus in a time frame similar to that of **adenovirus** alone. Transgene expression is always enhanced with FGF2-mediated delivery, whether overall transduction of the population is increased, equivalent, or decreased relative to nontargeted **adenoviral** vectors. However, the increase in transgene expression does not correlate quantitatively with enhanced cellular entry, indicating that other factors may influence transgene expression levels. The increase in transgene expression occurs only when the FGF2-retargeting moiety is physically complexed with the **adenoviral** vector, indicating a requirement for a spatial link between the **ligand** and the virus particle. The FGF2-**adenoviral** complex activates the FGF receptor-mediated proliferative signaling cascade, but this signal transduction is not required for the enhanced level of gene expression observed after FGF2-mediated delivery. These findings emphasize that, in addition to altering receptor tropism, the influence of FGF2 retargeting extends to intracellular **adenoviral** trafficking pathways.

Although the increased delivery of virions into the cell and nucleus contributes to the enhanced transgene expression observed with FGF2 retargeting, other as yet undefined cellular mechanisms also contribute to this process.

L4 ANSWER 2 OF 7 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001332370 MEDLINE
DOCUMENT NUMBER: 21295022 PubMed ID: 11402301
TITLE: Influence of **adenoviral** fiber mutations on viral encapsidation, infectivity and in vivo tropism.
AUTHOR: Leissner P; Legrand V; Schlesinger Y; Hadji D A; van Raaij M; Cusack S; Pavirani A; Mehtali M
CORPORATE SOURCE: Transgene SA, Strasbourg, France.
SOURCE: GENE THERAPY, (2001 Jan) 8 (1) 49-57.
Journal code: CCE; 9421525. ISSN: 0969-7128.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010625
Last Updated on STN: 20010625
Entered PubMed: 20010612
Entered Medline: 20010621

AB Targeting of **adenovirus** (**Ad**)-encoded therapeutic genes to specific cell types has become a major goal in gene therapy. Redirecting the specificity of infection requires the abrogation of the natural interaction between the viral fiber and its cellular receptors (CAR) and the simultaneous introduction of a new binding specificity into the **viral capsid**.
To abrogate the natural affinity of the fiber, we have mutated residues presumed to be directly or indirectly involved in CAR-binding in the knob domain of the fiber protein. These residues are located in the AB loop (Ser408) and in the DG loop (Tyr491, Ala494, Ala503). The mutations Ser408Glu, Tyr491Asp, Ala494Asp and Ala503Asp did not prevent the incorporation of trimeric fibers in the **viral capsid** but led to loss of CAR binding in vitro. Infectivity of the mutant viruses could be restored in vitro by introducing a **ligand** at the C-terminal end of the knob, confirming that the reduced infectivity of the fiber-modified virus was due to an impaired interaction of the viral particle with the CAR receptor. However, after systemic delivery, the in vivo biodistribution of impaired CAR-binding viruses without addition of a specific **ligand** was not altered when compared with wild-type **Ad**.

L4 ANSWER 3 OF 7 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001336866 MEDLINE

DOCUMENT NUMBER: 21010714 PubMed ID: 11127582
TITLE: Recombinant **adenovirus** vectors with knobless fibers for targeted gene transfer.
AUTHOR: van Beusechem V W; van Rijswijk A L; van Es H H; Haisma H J; Pinedo H M; Gerritsen W R
CORPORATE SOURCE: Department of Medical Oncology, University Hospital Vrije Universiteit, Amsterdam, The Netherlands.
SOURCE: GENE THERAPY, (2000 Nov) 7 (22) 1940-6. Journal code: CCE; 9421525. ISSN: 0969-7128.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered PubMed: 20001220
Entered Medline: 20010614

AB **Adenoviral** vector systems for gene therapy can be much improved by targeting vectors to specific cell types. This requires both the complete ablation of native **adenovirus** tropism and the introduction of a novel binding affinity in the **viral capsid**. We reasoned that these requirements could be fulfilled by deleting the entire knob domain of the **adenovirus** fiber protein and replacing it with two distinct moieties that provide a trimerization function for the knobless fiber and specific binding to the target cell, respectively. To test this concept, we constructed **adenoviral** vectors carrying knobless fibers comprising the alpha-helix trimerization domain from MoMuLV envelope glycoprotein. Two mimic targeting **ligands**, a Myc-epitope and a 6His-tag, were attached via a flexible linker peptide. The targeted knobless fiber molecules were properly expressed and imported into the nucleus of **adenovirus** packaging cells, where they were incorporated as functional trimers into the **adenovirus** capsid. Both **ligands** were exposed on the surface of the virion and were available for specific binding to their target molecules. Moreover, the knobless fibers mediated gene delivery into cells displaying receptors for the coupled **ligand**. Hence, these knobless fibers are prototype substrates for versatile addition of targeting **ligands** to generate truly targeted **adenoviruses**.

L4 ANSWER 4 OF 7 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001215872 MEDLINE
DOCUMENT NUMBER: 21144940 PubMed ID: 11249755
TITLE: Biophysical targeting of **adenovirus** vectors for gene therapy.
AUTHOR: Silman N J; Fooks A R

CORPORATE SOURCE: Centre for Applied Microbiology and Research, Salisbury, Wiltshire, SP4 0JG, UK..
nigel.silman@camr.org.uk
SOURCE: Curr Opin Mol Ther, (2000 Oct) 2 (5) 524-31. Ref: 70
Journal code: D0M; 100891485. ISSN: 1464-8431.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20010425
Entered PubMed: 20010315
Entered Medline: 20010419

AB Advances in understanding the interaction of animal viruses with their cognate receptors has led to improvements in the development of cell-specific, targeted viral vectors. Research strategies to generate safe, non-inflammatory viral vectors that are capable of delivering a therapeutic gene to a specific population of cells are currently underway in many laboratories. One approach in the utilization of this cell targeting activity is to ablate the natural interaction of the virus with its native receptor, although this is not an absolute requirement. The initial development of 'viral targeting strategies' was based on the view that by modifying the viral protein/receptor interaction, it would be possible to redirect virus vectors to new host cells. As the understanding of virus/cell interactions increased it was observed, however, that many viruses can use different entry mechanisms for cell attachment and penetration. **Adenovirus** vectors have been used extensively for the delivery of genes to cells. The entry mechanism for **adenoviruses** into cells has recently been studied and is relatively well understood, however, there are many aspects of cell receptor/virus interactions, which have still to be elucidated. The single high-affinity receptor on mammalian cells for **adenovirus** type 5 is recognized as the coxsackie and **adenovirus** receptor. However, in the absence of coxsackie and **adenovirus** receptor other receptors are used. A thorough understanding of the biology of **adenoviruses** is essential in the further development of their use as vectors for cell targeting. One strategy is to modify the **viral capsid**, either through coating the surface using bispecific antibodies, or by chemically crosslinking the targeting **ligand** onto the virion surface. Another approach is to genetically modify the virus by incorporating the targeting **ligand** into the viral 'spike' (fiber) protein. This involves manipulating the **adenovirus** genome and generating a new

targeting **ligand** on the surface of the fiber protein using recombinant DNA technology. The penton base protein has also received attention as a means of directing **adenoviruses** via insertion of novel targeting **ligands**.

L4 ANSWER 5 OF 7 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2000031165 MEDLINE
DOCUMENT NUMBER: 20031165 PubMed ID: 10566889
TITLE: Modification of an **adenoviral** vector with biologically selected peptides: a novel strategy for gene delivery to cells of choice.
COMMENT: Comment in: Hum Gene Ther. 1999 Nov 1;10(16):2575-6
AUTHOR: Romanczuk H; Galer C E; Zabner J; Barsomian G; Wadsworth S C; O'Riordan C R
CORPORATE SOURCE: Genzyme Corporation, Framingham, MA 01701, USA.. hromanczuk@genzyme.com
CONTRACT NUMBER: PPG 51670 (OAPP)
SOURCE: HUMAN GENE THERAPY, (1999 Nov 1) 10 (16) 2615-26. Journal code: A12; 9008950. ISSN: 1043-0342.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991216

AB Recombinant **adenoviruses** are currently being used as vectors for gene delivery to a wide variety of cells and tissues. Although generally efficacious for gene transfer in vitro, improvement in the efficiency of vector delivery in vivo may aid several gene therapy applications. One major obstacle is the lack of high-affinity viral receptors on the surface of certain cells that are targets for gene therapy. In principle, incorporation of avid, cell-specific **ligands** into the virion could markedly improve vector entry into the desired tissues. We have developed a strategy for addressing this issue in the lung by biopanning differentiated, ciliated airway epithelial cells against a phage display library. The peptide with the most effective binding was coupled to the surface of an **adenovirus** using bifunctional polyethylene glycol (PEG) molecules. The chemically modified **adenoviral** vector was able to effect gene transfer to well-differentiated human airway epithelial cells by an alternative pathway dependent on the incorporated peptide. Coupling of PEG to the surface of the virus also served to partially protect the virus from neutralizing antibodies in vitro. These experiments will aid in the design of improved **adenoviral** vectors with the capacity for more specific and efficient delivery of therapeutic

genes to desired target tissues. We have used a novel method for enhancing gene delivery to target cells by coupling a biologically selected peptide to the surface of an **adenovirus** with bifunctional PEG molecules. Modification of the **viral capsid** by the addition of a peptide with binding preference for differentiated ciliated airway epithelia allowed gene delivery to those cells by a novel entry pathway. Incorporation of the CFTR gene in a similarly modified vector resulted in correction of defective Cl- transport in well-differentiated epithelial cultures established from human cystic fibrosis (CF) donors. The presence of PEG molecules on the surface of the virus served, in addition, to reduce antibody neutralization. Modification of **adenoviruses** with PEG/peptide complexes can serve to partially overcome the barrier of inefficient gene transfer in some cell types and some of the adverse immunological responses associated with gene delivery by these vectors.

L4 ANSWER 6 OF 7 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 6
ACCESSION NUMBER: 1998107644 EMBASE
TITLE: Transient immunosuppression allows transgene expression following readministration of adeno-associated viral vectors.
AUTHOR: Manning W.C.; Zhou S.; Bland M.P.; Escobedo J.A.; Dwarki V.
CORPORATE SOURCE: Dr. V. Dwarki, Chiron Corporation, 4560 Horton Street, Emeryville, CA 94608, United States
SOURCE: Human Gene Therapy, (1 Mar 1998) 9/4 (477-485). Refs: 39
ISSN: 1043-0342 CODEN: HGTHE3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Adeno-associated viral (AAV) vectors have much promise in gene therapy. Among the many properties that make AAV an ideal vector for gene therapy are its ability to infect both dividing and nondividing cells and the longevity of expression in tissues such as brain, skeletal muscle, and liver. However, like other viral vectors, readministration of vector is limited because of the host's immune response to viral components of the vector. Using class I, class II, and CD40 **ligand** (CD40L)-deficient mice, we demonstrate that neutralizing antibodies to the **viral capsid** proteins prevent transgene expression following readministration of

rAAV vectors. Transient immunosuppression of mice by treatment with antibody to CD4 at the time of primary infection allowed transgene expression after readministration of rAAV vectors to animals. Transient immunesuppression with antibody to CD40L had only a modest effect on the efficacy of readministration. The ability to readminister virus was inversely correlated with both AAV capsid enzyme-linked immunosorbent assay titers and AAV neutralizing antibody titers. These studies demonstrate that readministration of rAAV can be accomplished by down regulating the anti-AAV immune response and suggest the use of repeated administration of rAAV as a viable form of therapy for the treatment of chronic diseases.

L4 ANSWER 7 OF 7 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1997-145702 [13] WPIDS
DOC. NO. CPI: C1997-046613
TITLE: Delivery of target genes to specific target cells - uses viral vectors expressing a gene of interest and a targetting moiety specific for target molecule of target cell.
DERWENT CLASS: B04 D16
INVENTOR(S): VALERIO, D; VAN BEUSECHEM, V W
PATENT ASSIGNEE(S): (INTR-N) INTROGENE BV
COUNTRY COUNT: 73
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9705266	A1	19970213	(199713)*	EN	53
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG					
W: AL AM AT AU AZ BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN					
AU 9665350	A	19970226	(199725)		
EP 840797	A1	19980513	(199823)	EN	
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT SE SI					
JP 11510050	W	19990907	(199947)		51
AU 727531	B	20001214	(200103)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9705266	A1	WO 1996-NL302	19960725
AU 9665350	A	AU 1996-65350	19960725
EP 840797	A1	EP 1996-925173	19960725

		WO 1996-NL302	19960725
JP 11510050	W	WO 1996-NL302	19960725
		JP 1997-507496	19960725
AU 727531	B	AU 1996-65350	19960725

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9665350	A	Based on	WO 9705266
EP 840797	A1	Based on	WO 9705266
JP 11510050	W	Based on	WO 9705266
AU 727531	B	Previous Publ.	AU 9665350
		Based on	WO 9705266

PRIORITY APPLN. INFO: EP 1995-202040 19950725
AN 1997-145702 [13] WPIDS
AB WO 9705266 A UPAB: 19991122
A method for delivering genetic material to a target cell comprises: (a) preparing a gene delivery vehicle (I) comprising a molecule encoding a gene of interest, a **viral capsid** or envelope and a first member (A) of a specific binding pair (pref. having no specific affinity for molecules associated with the surface of the target cell); (b) preparing a conjugate comprising the complementary member (B) of (A) and a molecule having affinity for a molecule associated with the surface of a target cell; (c) contacting (I) with the conjugate so that (A) and (B) bind; and (d) delivering the complex of conjugate and (I) to the target cell. Also claimed are: (1) a gene delivery vehicle (I) as above that has no specific affinity for molecules associated with the surface of the target cell; (2) a conjugate as in (b); and (3) a complex of (I) and the conjugate as in (d).

The binding pair is selected from: (a) an immunoglobulin present on the cell surface target cell and an immunoglobulin binding moiety that binds to a constant region on the immunoglobulin, esp. protein A, protein G or an Fc receptor; (b) biotin and either avidin or streptavidin; and (c) a receptor and **ligand**. The gene delivery vehicle is pref. derived from an **adenovirus**, adeno-associated virus or retrovirus.

USE - The method is used for targetting specific genes to specific target cells. Kits are provided in which there may be a multitude of different conjugates comprising the same target member but a number of different targetting moieties (claimed).
Dwg.3/5

(FILE 'MEDLINE' ENTERED AT 12:19:10 ON 29 JUN 2001)
L5 22705 SEA FILE=MEDLINE ABB=ON PLU=ON LIGANDS/CT
L6 9466 SEA FILE=MEDLINE ABB=ON PLU=ON ADENOVIRIDAE/CT

L7 36 SEA FILE=MEDLINE ABB=ON PLU=ON L5 AND L6
L8 8946 SEA FILE=MEDLINE ABB=ON PLU=ON CAPSID/CT
L9 2 SEA FILE=MEDLINE ABB=ON PLU=ON L7 AND L8

L9 ANSWER 1 OF 2 MEDLINE
AN 1999445818 MEDLINE
TI Construction of a pseudoreceptor that mediates transduction by adenoviruses expressing a ligand in fiber or penton base.
AU Einfeld D A; Brough D E; Roelvink P W; Kovesdi I; Wickham T J
SO JOURNAL OF VIROLOGY, (1999 Nov) 73 (11) 9130-6.
Journal code: KCV; 0113724. ISSN: 0022-538X.
AB Modification of adenovirus to achieve tissue specific targeting for the delivery of therapeutic genes requires both the ablation of its native tropism and the introduction of specific, novel interactions. Inactivation of the native receptor interactions, however, would cripple the virus for growth in production cells. We have developed an alternative receptor, or pseudoreceptor, for the virus which might allow propagation of viruses with modified fiber proteins that no longer bind to the native adenovirus receptor (coxsackievirus/adenovirus receptor [CAR]). We have constructed a membrane-anchored single-chain antibody [m-scFv(HA)] which recognizes a linear peptide epitope (hemagglutinin [HA]). Incorporation of HA within the HI loop of the fiber protein enabled the modified virus to transduce pseudoreceptor expressing cells under conditions where fiber-CAR interaction was blocked or absent. The pseudoreceptor mediated virus transduction with an efficiency similar to that of CAR. In addition, the HA epitope mediated virus transduction through interaction with the m-scFv(HA) when it was introduced into penton base. These findings indicate that cells expressing the pseudoreceptor should support production of HA-tagged adenoviruses independent of retaining the fiber-CAR interaction. Moreover, they demonstrate that high-affinity targeting ligands may function following insertion into either penton base or fiber.

L9 ANSWER 2 OF 2 MEDLINE
AN 94220051 MEDLINE
TI Biochemical and functional analysis of an adenovirus-based ligand complex for gene transfer.
AU Fisher K J; Wilson J M
SO BIOCHEMICAL JOURNAL, (1994 Apr 1) 299 (Pt 1) 49-58.
Journal code: 9YO; 2984726R. ISSN: 0264-6021.
AB Ligand-mediated approaches to gene transfer offer an alternative to viral vectors for both in vivo and in vitro applications. Although a significant percentage of the plasmid-based DNA complex is lost to lysosomal degradation following receptor-mediated endocytosis, simultaneous infection with adenovirus has been shown to increase the level of transgene expression [Curiel, Agarwal, Wagner and Cotten (1991) Proc. Natl. Acad. Sci. U.S.A. 88, 8850-8854; Wagner,

Zatloukal, Cotten, Kirlappos, Mechtler, Curiel and Birnstiel (1992) Proc. Natl. Acad. Sci. U.S.A. 89, 6099-6103]. In this study we describe an adenovirus-based ligand complex where the plasmid DNA, polycation-ligand conjugate and adenovirus are contained within a single particle structure. At the core of the transfection particle is a replication-defective recombinant adenovirus encoding a cDNA minigene for human placenta alkaline phosphatase that was chemically modified with poly(L-lysine) (Ad-pLys). Electron microscopy of an adenovirus-based ligand complex formed by successively adding plasmid DNA and an asialo-orosomucoid-poly(L-lysine) conjugate to Ad-pLys revealed structures that appeared as intact viral particles coated with a dense biomolecular layer. Adenovirus-based ligand complexes containing either a luciferase or beta-galactosidase reporter plasmid were shown to efficiently deliver the plasmid transgene to cells that express the hepatic asialoglycoprotein receptor. Furthermore, the poly(L-lysine) modification greatly reduced the infectivity potential of the virus without causing a concomitant loss of augmented gene transfer. As an alternative to infectious virions, incomplete products of viral assembly were also considered as a source for endosomalytic activity. However, these defective virions were unable to significantly enhance plasmid transgene delivery.

FILE 'CAPLUS' ENTERED AT 12:24:57 ON 29 JUN 2001)
L10 366 SEA FILE=CAPLUS ABB=ON PLU=ON (AD(S)ADENOVIR? OR ADENOVIR? OR ADENO VIR?) AND CAPSID(5A)(VIR? OR PROTEIN)
L11 29 SEA FILE=CAPLUS ABB=ON PLU=ON L10 AND LIGAND

=> s l11 not l2
L12 20 L11 NOT L2

L12 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:396882 CAPLUS
DOCUMENT NUMBER: 135:24659
TITLE: THALWHT peptides for gene targeting to airway epithelium
INVENTOR(S): Coutelle, Charles; Jost, Philipp Jakob; Schneider, Holm
PATENT ASSIGNEE(S): Imperial College Innovations Limited, UK
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001038346 A2 20010531 WO 2000-GB4409 20001120
W: JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR
PRIORITY APPLN. INFO.: GB 1999-27769 A 19991124

AB Targeted gene delivery into human airway epithelial cells may help to overcome the current inefficiency of gene transfer as the major problem confronting cystic fibrosis gene therapy. To elucidate novel **ligands** targeting abundant, apically located receptors on differentiated airway epithelial cells, a random peptide phage display library was screened for peptides binding with high affinity to such cells. This screening yielded a selectively enriched amino acid sequence, Thr-His-Ala-Leu-Trp-His-Thr (THALWHT). Subsequent binding studies revealed that THALWHT-displaying phages bound much stronger than phages displaying control peptides to the two human airway epithelial cell lines tested, whereas on a variety of non-airway-derived human cell lines no significant binding differences were obsd., suggesting selective binding of the THALWHT-motif to airway epithelia. A synthetic peptide comprising a cyclic CTHALWHTC domain and a DNA-binding moiety of 16 lysine residue was shown to enable efficient, targeted gene delivery into human airway epithelial cell lines.

L12 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:354727 CAPLUS
TITLE: A simplified system for constructing recombinant **adenoviral** vectors containing heterologous peptides in the HI loop of their fiber knob
AUTHOR(S): Mizuguchi, H.; Koizumi, N.; Hosono, T.; Utoguchi, N.; Watanabe, Y.; Kay, M. A.; Hayakawa, T.
CORPORATE SOURCE: Division of Biological Chemistry and Biologicals, National Institute of Health Sciences, Tokyo, 158-8501, Japan
SOURCE: Gene Ther. (2001), 8(9), 730-735
CODEN: GETHEC; ISSN: 0969-7128
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The use of recombinant **adenovirus** (**Ad**) vectors contg. genetically modified **capsid proteins** is an attractive strategy for achieving targeted gene transfer. The HI loop of the fiber knob is a promising candidate location for the incorporation of foreign **ligands** for achieving this goal. However, the method of constructing an Ad vector contg. a foreign **ligand** in the HI loop of the fiber knob has proved difficult. In this study, we developed a simple system to construct

fiber-modified vectors. To do this, a vector plasmid contg. a complete E1/E3-deleted Ad type 5 genome and a unique Csp45I and/or ClaI site between positions 32679 and 32680 of the Ad genome (residues threonine-546 and proline-547 of the fiber protein) was constructed. Oligonucleotides corresponding to the Arg-Gly-Asp (RGD) or Asn-Gly-Arg (NGR)-contg. peptide motif (as a model) and contg. a Csp45I and/or ClaI recognition site, were ligated into the Csp45I and/or ClaI-digested plasmid. The foreign transgene expression cassette was inserted into the E1 deletion site of the vector plasmid and the fiber-mutant Ad vector was produced by transfection of the PacI-digested plasmid into 293 cells. The virus contg. the RGD or NGR peptide on the fiber knob was able to infect human glioma cells, which do not express coxsackievirus and **adenovirus** receptor (CAR), one of the **Ad** virus receptors, about 100-1000 times more efficient than the virus contg. wild-type fiber. This suggested that the mutant virus mediated CAR-independent cell entry pathway. The simplicity of this method allows not only for easy construction of fiber-mutant Ad vectors, but also for screening of the peptides that target the vector to the desired cells and tissues.

REFERENCE COUNT: 37

REFERENCE(S):
(1) Arap, W; Science 1998, V279, P377 CAPLUS
(2) Asaoka, K; J Neurosurg 2000, V92, P1002 CAPLUS
(3) Bai, M; J Virol 1993, V67, P5198 CAPLUS
(4) Barry, M; Nat Med 1996, V2, P299 CAPLUS
(5) Bergelson, J; Science 1997, V275, P1320 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:297753 CAPLUS

TITLE: Genetic targeting of an **adenovirus** vector via replacement of the fiber protein with the phage T4 fibritin

AUTHOR(S): Krasnykh, Victor; Belousova, Natalya; Korokhov, Nikolay; Mikheeva, Galina; Curiel, David T.

CORPORATE SOURCE: Division of Human Gene Therapy, Departments of Medicine, Pathology and Surgery, University of Alabama at Birmingham, and VectorLogics, Inc., Birmingham, AL, 35294, USA

SOURCE: J. Virol. (2001), 75(9), 4176-4183
CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The utility of **adenovirus** (**Ad**) vectors for gene therapy is restricted by their inability to selectively transduce

disease-affected tissues. This limitation may be overcome by the derivation of vectors capable of interacting with receptors specifically expressed in the target tissue. Previous attempts to alter Ad tropism by genetic modification of the Ad fiber have had limited success due to structural conflicts between the fiber and the targeting **ligand**. Here we present a strategy to derive an Ad vector with enhanced targeting potential by a radical replacement of the fiber **protein** in the Ad **capsid** with a chimeric mol. contg. a heterologous trimerization motif and a receptor-binding **ligand**. Our approach, which capitalized upon the overall structural similarity between the human Ad type 5 (Ad5) fiber and bacteriophage T4 fibritin proteins, has resulted in the generation of a genetically modified Ad5 incorporating chimeric fiber-fibritin proteins targeted to artificial receptor mols. Gene transfer studies employing this novel viral vector have demonstrated its capacity to efficiently deliver a transgene payload to the target cells in a receptor-specific manner.

REFERENCE COUNT: 34

REFERENCE(S):
(1) Bergelson, J; Science 1997, V275, P1320 CAPLUS
(2) Bewig, B; BioTechniques 2000, V28, P870 CAPLUS
(3) Chartier, C; J Virol 1996, V70, P4805 CAPLUS
(4) Chroboczek, J; Curr Top Microbiol Immunol 1995, V199, P163 CAPLUS
(5) Davison, E; J Virol 1999, V73, P4513 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:384227 CAPLUS
DOCUMENT NUMBER: 133:29600
TITLE: Capsid particles of hepatitis B core antigen for presentation of immunogenic components
INVENTOR(S): Murray, Kenneth
PATENT ASSIGNEE(S): Biogen, Inc., USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000032625	A1	20000608	WO 1999-US28755	19991203

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,

LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-110911 P 19981204

AB The authors discloses the use of hepatitis B virus (HBV) core antigen particles for presentation to the immune system of multiple immunogen specificities. The immunogens, epitopes, or other related structures, are crosslinked or fused to HBV capsid-binding peptides that selectively bind to HBV core protein. Mixts. of different immunogens and/or capsid-binding peptide **ligands** may be crosslinked to the same HBV core particle. Such resulting multicomponent or multivalent HBV core particles may be advantageously used in therapeutic and prophylactic vaccines and compns., as well as in diagnostic applications.

REFERENCE COUNT: 8

REFERENCE(S):

(1) Bottcher, B; EMBO JOURNAL 1998, V17(23), P6839 CAPLUS
(2) Dyson, M; WO 9818818 A 1998 CAPLUS
(3) Murray, K; BIOLOGICAL CHEMISTRY 1999, V380(3), P277 CAPLUS
(7) Scripps Clinic Res; EP 0271302 A 1988 CAPLUS
(8) Ulrich, R; ADVANCES IN VIRUS RESEARCH 1998, V50, P141 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:468633 CAPLUS

DOCUMENT NUMBER: 131:98495

TITLE: **Adenoviral** vectors with **capsid proteins** modified to include tissue-targeting **ligands**

INVENTOR(S): Romanczuk, Helen; Armentano, Donna; O'Riordan, Catherine R.

PATENT ASSIGNEE(S): Genzyme Corporation, USA

SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9936545	A2	19990722	WO 1999-US913	19990115
WO 9936545	A3	19991104		

W: AU, CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

AU 9923219	A1	19990802	AU 1999-23219	19990115
EP 1044274	A2	20001018	EP 1999-903122	19990115

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.: US 1998-71674 P 19980116
WO 1999-US913 W 19990115

AB The present invention is directed to **adenoviral** vectors having modified **capsid proteins** which comprise heterologous **ligands** that improve and/or alter the infectious capability of the vector. Such **ligands** are capable of binding to target cells, and their inclusion into **adenoviral** vectors facilitates the binding and infectious properties of the vectors. In a preferred embodiment, the **ligands** are peptides, and the target cells are epithelial cells. The invention is also directed to novel heterologous **ligands**, to **ligand**-receptor complexes, and to compns. comprising the **adenoviral** vectors of the invention. Thus **ligands** with known interaction for a cellular receptor or a nuclear entry pathway are substituted into the hypervariable domain of hexon loop 1: the RGD sequences from adenotypes 2 and 5 (His-Ala-Ile-Arg-Gly-Asp-Thr-Phe-Ala), or type 17 (Gly-Pro-Ala-Arg-Gly-Asp-Ser-Ser-Val), as well as the basic stretch of amino acids within the SV40 large T antigen that targets that protein to the nucleus (Pro-Lys-Lys-Lys-Arg-Lys-Val). Addnl. aspects of the invention include methods to use the **adenoviral** vectors of the invention to deliver transgenes to target cells.

L12 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:344861 CAPLUS
DOCUMENT NUMBER: 131:4240
TITLE: Immunoglobulin molecules having a synthetic variable region and modified specificity
INVENTOR(S): Burch, Ronald M.
PATENT ASSIGNEE(S): Euro-Celtique, S.A., Bermuda
SOURCE: PCT Int. Appl., 123 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9925378	A1	19990527	WO 1998-US24302	19981113

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

WO 9925379 A1 19990527 WO 1998-US24303 19981113
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9914597 A1 19990607 AU 1999-14597 19981113
AU 9914598 A1 19990607 AU 1999-14598 19981113
EP 1030684 A1 20000830 EP 1998-958584 19981113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
EP 1032420 A1 20000906 EP 1998-958583 19981113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.: US 1997-65716 P 19971114
US 1998-81403 P 19980410
WO 1998-US24302 W 19981113
WO 1998-US24303 W 19981113

AB The invention provides modified Ig mols., particularly antibodies, that immunospecifically bind a first member of a binding pair which binding pair consists of the first member and a second member, which Igs have a variable domain contg. one or more complimentary detg. regions that contain the amino acid sequence of a binding site for the second member of the binding pair. The first member is a tumor antigen or an antigen of an infectious disease agent, and the second member is a mol. on the surface of an immune cell. The invention further provides for therapeutic and diagnostic use of the modified Ig.

REFERENCE COUNT: 13
REFERENCE(S):
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(3) Brumeanu; Journal Experimental Medicine 1993, V178, P1795 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:271508 CAPLUS
DOCUMENT NUMBER: 130:292442
TITLE: Biotinylated **adenoviral** vectors and their use for targeted delivery of genes
INVENTOR(S): Spence, Sally E.; Keller, Jonathan R.; Smith, Jeffrey S.
PATENT ASSIGNEE(S): The Government of the United States of America, Department of Health and Human Services, USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9919500	A1	19990422	WO 1998-US21364	19981009
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9896924	A1	19990503	AU 1998-96924	19981009

PRIORITY APPLN. INFO.: US 1997-61587 P 19971010
WO 1998-US21364 W 19981009

AB The invention provides recombinant viral vectors for targeted delivery of genes to selected cells, wherein the recombinant virus is a small, encapsidated virus, such as **adenovirus** or adeno-assocd. virus. The invention includes a protocol for producing these vectors, whereby biotin is covalently linked to the **capsid** of said **virus** particles, yet wild-type infectivity of the recombinant virus is maintained. Streptavidin is used to link the biotinylated recombinant virus to a biotinylated **ligand** or antibody that could be used to target this vector to any cell type. Versatility of the vector of this invention was demonstrated by substituting targeting moieties (antibodies to four different cell surface markers for steel factor), which resulted in

targeted gene transfer to cell lines expressing those specific markers.

REFERENCE COUNT: 7

REFERENCE(S):
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(3) Introgene BV; WO 9705266 A 1997 CAPLUS
(5) Roux, P; Proceedings of the National Academy of Sciences of USA 1989, V86(23), P9079 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:63172 CAPLUS
DOCUMENT NUMBER: 130:234583
TITLE: Fiberless recombinant **adenoviruses**: virus maturation and infectivity in the absence of fiber
AUTHOR(S): Legrand, V.; Spehner, D.; Schlesinger, Y.; Settelen, N.; Pavirani, A.; Mehtali, M.
CORPORATE SOURCE: Transgene S.A., Strasbourg, 67000, Fr.
SOURCE: J. Virol. (1999), 73(2), 907-919
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In vivo targeting of therapeutic genes to specific tissues has become a major issue in gene therapy, in particular when recombinant **adenovirus** vectors are used. Restriction of the viral tropism to selected cell types requires the abrogation of the interaction between the viral fiber and its natural cellular receptors and the introduction of a new binding specificity into the virion. In this context, fiberless **adenoviruses** are attractive vectors, since they may be used as substrates for the insertion of a new **ligand** in other **capsid proteins**. In this study, the authors confirm by using cloned full-length **adenovirus** genomes with the fiber gene deleted that efficient virus particle formation can occur in the absence of fiber. As expected, the infectivity of such fiberless viruses was severely reduced, but it could be only partially restored when the viruses were produced in cells stably providing the fiber in trans. Although incorporation of penton base into the fiberless particles was normal and binding of the particles to the cellular integrins was functional, several pieces of exptl. evidence suggest that later steps in the cell entry process are impaired in correlation with an incorrect maturation of several structural

proteins of the fiberless particles. These observations support the hypothesis that the fiber protein may have addnl. biol. functions besides its role in cell binding. Together with the fiber complementation cells, such fiberless vectors constitute unique tools to investigate the role of the fiber in virus assembly, maturation, and cell entry and to explore the possibility of deriving gene transfer vectors with novel target specificities.

REFERENCE COUNT: 65
REFERENCE(S):
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:640334 CAPLUS
DOCUMENT NUMBER: 129:255990
TITLE: **Adenoviral** vectors with chimeric fiber proteins for altered cell tropism as well as vector purification
INVENTOR(S): Curiel, David T.; Krasnykh, Victor; Dimitriev, Igor
PATENT ASSIGNEE(S): UAB Research Foundation, USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9841618	A1	19980924	WO 1998-US3879	19980313
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9864429	A1	19981012	AU 1998-64429	19980313

PRIORITY APPLN. INFO.: US 1997-40703 19970314
US 1997-54112 19970729
WO 1998-US3879 19980313

AB The utility of current recombinant **adenovirus** vectors for gene therapy applications is improved by designing targeted vectors capable of gene delivery to selected cell types in vivo. In order to achieve such targeting, incorporation of **ligands** in the **adenoviral** fiber protein, in which the protein mediates primary binding of **adenovirus** to its cell surface receptor, utilizes the HI loop of the fiber knob as a convenient locale for incorporation of heterologous **ligands**. Recombinant fiber proteins expressed in a variety of cells including baculovirus-infected insect cells and E. coli to demonstrate that the incorporation of the FLAG octapeptide into the HI loop does not ablate fiber trimerization and does not disturb formation of the cell-binding site localized in the knob. A recombinant **adenovirus** of the instant invention having this modified fiber shows that a short peptide sequence engineered in the knob is compatible with the biol. functions of the fiber. A peptide incorporated into the knob according to the invention remains available for binding in the context of mature virions contg. modified fibers. The invention incorporates heterologous **ligands** into the HI loop of the fiber knob and the properties of this locale are consistent with its employment in **adenovirus** re-targeting strategies.

L12 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:696665 CAPLUS
DOCUMENT NUMBER: 127:362602
TITLE: Targeted viral genetic vectors
INVENTOR(S): Mamounas, Michael; Yu, Gang; Yang, Qicheng; Li, Qi-xiang; Barber, Jack; Yu, Mang
PATENT ASSIGNEE(S): Immusol Incorporated, USA; Mamounas, Michael; Yu, Gang; Yang, Qicheng; Li, Qi-Xiang; Barber, Jack; Yu, Mang
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9738723	A1	19971023	WO 1997-US6590	19970415

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO,

NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

CA 2251738	AA	19971023	CA 1997-2251738	19970415
AU 9726780	A1	19971107	AU 1997-26780	19970415
EP 927044	A1	19990707	EP 1997-918752	19970415

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.: US 1996-15497 19960416
WO 1997-US6590 19970415

AB Viral vectors are targeted to selected cell types by blocking the wild-type viral cell binding site and incorporating a targeting agent into the vector particle. The targeting agent binds to the selected cell type by binding a mol. on the surface of the cell, or by binding a second targeting agent which binds the selected cell. Parvovirus, retrovirus, Herpes virus and Ad virus based vectors are provided. Libraries of viral vectors having the targeting agent are provided. Methods of selecting recombinant viral vectors from the libraries are also provided. Polypeptide **ligands** isolated from libraries of phage or viral vectors are provided.

L12 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:510223 CAPLUS
DOCUMENT NUMBER: 127:105243
TITLE: Fusion proteins of viral surface proteins and **ligands** for LDL receptor superfamily members for targetting of materials to specific cell types
INVENTOR(S): Rosenberg, Steven
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9724453	A1	19970710	WO 1996-US19196	19961202
EP 880596	A1	19981202	EP 1996-946385	19961202

W: CA, JP, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPLN. INFO.: US 1995-580139 19951228
WO 1996-US19196 19961202

AB A method of displaying **ligands** for cell type-specific receptors on the surface of a virus or a non-viral particle such as a liposome using fusion proteins of the **ligand** and a viral surface protein is described. Specifically, **ligands** for member of the LDL receptor family are used. Particles carrying these fusion proteins can be internalized by the target cells for delivery of nucleic acids. Examples include fusion proteins of a serpin, for example PAI-1, for targeting cells presenting urokinase receptor with bound urokinase. Cell specific gene therapy is possible using these methods and materials.

L12 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:215792 CAPLUS
DOCUMENT NUMBER: 126:196103
TITLE: Viral vectors with modified surfaces and their use in the targetting of transforming DNA to specific cell types
INVENTOR(S): Valerio, Domenico; Van Beusechem, Victor Willem
PATENT ASSIGNEE(S): Introgene B.V., Neth.; Valerio, Domenico; Van Beusechem, Victor Willem
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9705266	A1	19970213	WO 1996-NL302	19960725
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM				
AU 9665350	A1	19970226	AU 1996-65350	19960725
AU 727531	B2	20001214		
EP 840797	A1	19980513	EP 1996-925173	19960725
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 11510050	T2	19990907	JP 1996-507496	19960725

PRIORITY APPLN. INFO.: EP 1995-202040 A 19950725
WO 1996-NL302 W 19960725

AB A method of delivering nucleic acids to a specific cell type using a viral vector with a modified viral surface is described. The **virus** has a modified **capsid** or envelope **protein** that presents a **ligand** for an intermediate

protein. The intermediate protein has two binding sites, one is for the new moiety presented on the virus and the other is for a moiety presented on the surface of the target cell. The virus becomes bound to the target cell surface by this intermediate protein. The use of this bipartite intermediate protein means that a new virus does not have to be designed for each new cell type. The viral surface is modified to minimize or eliminate virus binding to its natural target. The moiety on the virus can be for example an Ig binding moiety (e.g. capable of binding to a Fc fragment, protein A, protein G, FcR or an anti-Ig antibody), or biotin, avidin or streptavidin. The outer membrane or **capsid** of the **virus** may contain a substance which mediates entrance of the gene delivery vehicle into the target cell. Due to the specificity of the **ligand**, the high affinity of the binding pair and to the inability of the gene delivery vehicle to be targeted when used alone, the universality of the method for gene delivery, together with its high cell type selectively can easily be achieved by the use of various targeting conjugates. The development of a Moloney murine leukemia virus with an Fc.gamma.RI Ig-binding domain on the viral surface is described.

L12 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:676262 CAPLUS
DOCUMENT NUMBER: 125:319219
TITLE: Immunology of gene therapy with **adenoviral** vectors in mouse skeletal muscle
AUTHOR(S): Yang, Yiping; Haecker, Sarah Ehlen; Su, Qin; Wilson, James M.
CORPORATE SOURCE: Inst. for Human Gene Therapy, Univ. Pennsylvania Medical Center and Wistar Inst., Philadelphia, PA, 19104, USA
SOURCE: Hum. Mol. Genet. (1996), 5(11), 1703-1712
CODEN: HMGEE5; ISSN: 0964-6906
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Skeletal muscle is an attractive target for somatic gene transfer of both acquired and inherited disorders. Direct injection of **adenoviral** vectors in the skeletal muscle leads to recombinant gene expression in a large no. of muscle fibers. Transgene expression has been transient in most organs and assocd. with substantial inflammation when expts. are performed in adult immune competent mice. In this report, we utilize a variety of in vivo and in vitro models of T and B cell function to characterize the nature of the immune response to **adenoviral** vectors injected into murine skeletal muscle. Cellular immunity dependent on CD4+ and CD8+ T cells contributes to the loss of recombinant gene expression and the development of localized inflammation. Antigen

specific activation of T cells occurs to both viral proteins and the reporter gene .beta.-galactosidase. Systemic levels of neutralizing antibody to the **capsid proteins** of the vector are also generated. Destructive immune responses responsible for loss of transgene expression are largely directed against .beta.-galactosidase in that transgene expression was stable when .beta.-galactosidase was eliminated as a neoantigen in mice transgenic for lacZ. A strategy to prevent the cellular and humoral immunity to this therapy was developed based on transiently ablating CD4+ T cell activation at the time of vector delivery. Encouraging results were obtained when vector was administered with one of several immune modulating agents including cyclophosphamide, mAb to CD4+ cells, and mAb to CD40 **ligand**. These studies indicate that cellular and humoral immune responses are elicited in the context of gene therapy directed to skeletal muscle with **adenoviral** vectors. Transient ablation of CD4+ T cell activation prevents the effector responses of the CD8+ T and B cells.

L12 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:495344 CAPLUS
DOCUMENT NUMBER: 125:140528
TITLE: Transient subversion of CD40 **ligand** function diminishes immune responses to **adenovirus** vectors in mouse liver and lung tissues
AUTHOR(S): Yang, Yiping; Su, Qin; Grewal, Iqbal S.; Schilz, Robert; Flavell, Richard A.; Wilson, James M.
CORPORATE SOURCE: Institute Human Gene Therapy, Wistar Institute, Philadelphia, PA, 19104, USA
SOURCE: J. Virol. (1996), 70(9), 6370-6377
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB First-generation **adenovirus** vectors will have limited application in gene therapy for chronic diseases because of destructive host immune responses. Important immune effectors include CD8+ T cells, which mediate target cell destruction and ablate transgene expression, and B cells, which produce neutralizing antibodies that block effective readministration of vector. Previous studies indicated that activation of CD4+ T cells by **virus capsid proteins** is necessary for full realization of effector function of CD8+ T cells and B cells. In this paper, we present a strategy for preventing CD4+ T-cell activation by an **adenovirus** vector delivered to mouse liver and lung tissues which is based on interfering with T-cell priming via CD40 **ligand**-CD40 interactions. **Adenovirus** transgene expression was stabilized in mice

genetically deficient in CD40 **ligand** (CD40L), and neutralizing antibody to **adenovirus** did not develop, allowing efficient readministration of vector. A transient blockade of T-cell activation with an antibody to CD40L infused into the animal at the time of **adenovirus** vector-mediated gene transfer led to stabilization of transgene expression and diminished prodn. of neutralizing antibody, allowing readministration of vector. In vitro T-cell assays suggested that a block in the primary activation of CD4+ T cells was responsible for the lack of B-cell- and cytotoxic-T-cell-dependent responses. This suggests a strategy for improving the potential of **adenovirus** vectors based on administration of an antibody to CD40L at the time of vector administration.

L12 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:171343 CAPLUS
DOCUMENT NUMBER: 124:228574
TITLE: **Adenovirus** type 5 and 7 capsid chimera: fiber replacement alters receptor tropism without affecting primary immune neutralization epitopes
AUTHOR(S): Gall, Jason; Kass-Eisler, Alyson; Leinwand, Leslie; Falck-Pedersen, Erik
CORPORATE SOURCE: Dep. Microbiology, Cornell Univ. College of Medicine, New York, NY, 10021, USA
SOURCE: J. Virol. (1996), 70(4), 2116-123
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The efficient uptake of **adenovirus** into a target cell is a function of **adenovirus capsid proteins** and their interaction with the host cell. The **capsid protein** fiber mediates high-affinity attachment of **adenovirus** to the target cell. Although the cellular receptor(s) for **adenovirus** is unknown, evidence indicates that a single receptor does not function as the attachment site for each of the 49 different serotypes of **adenovirus**. Sequence variation of the fiber **ligand**, particularly in the C-terminal knob domain, is assocd. with serotype-specific binding specificity. Addnl., this domain of fiber functions as a major serotype determinant. Fiber involvement in cell targeting and its function as a target of the host immune response make the fiber gene an attractive target for manipulation, both from the perspective of **adenovirus** biol. and from the perspective of using **adenovirus** vectors for gene transfer expts. A defective chimeric **adenovirus** type 5 (Ad5) reporter virus was generated by replacing the Ad5 fiber gene with the fiber gene from Ad7A. The chloramphenicol acetyltransferase reporter gene was

used to characterize this virus with respect to infectivity both in vitro and in vivo. Also, the role of antifiber antibody in the host neutralizing immune response to **adenovirus** infection was characterized. These studies demonstrate that exchange of fiber is a strategy that will be useful in characterizing receptor tropism for different serotypes of **adenovirus**. Addnl., the neutralizing immune response to Ad5 and Ad7 does not differentiate between 2 viruses that differ only in their fiber proteins. Therefore, following a primary **adenovirus** inoculation, antibodies generated against fiber do not constitute a significant fraction of the neutralizing antibody population.

L12 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:908599 CAPLUS
DOCUMENT NUMBER: 123:334461
TITLE: Protein **ligands** of the human **adenovirus** type 2 outer capsid identified by biopanning of a phage-displayed peptide library on separate domains of wild-type and mutant penton capsomers
AUTHOR(S): Hong, Saw See; Boulanger, Pierre
CORPORATE SOURCE: Lab. Virologie Pathogenese Moleculaires, Inst. Biologie, Montpellier, 34060, Fr.
SOURCE: EMBO J. (1995), 14(19), 4714-27
CODEN: EMJODG; ISSN: 0261-4189
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A filamentous phage-displayed random hexapeptide library was screened on the **adenovirus** type 2 (Ad2) penton capsomer and its sep. domains, penton base, full-length fiber, fiber shaft, and fiber knob. Affinity supports were designed to immobilize the penton ligate with a preferred orientation, via immunoadsorption to pre-coated antibody. Three classes of phagotopes were distinguished in the eluates from the penton and fiber domains. The 1st class represented peptide sequences identified in certain Ad2 **capsid proteins**, **protein** IIIa, **protein** pVIII, penton base, and penton fiber. Data from specific **ligand** elution of phages bound to fiber and penton base wild types and mutants suggested that the region overlapping the RLSNLLG motif at residues 254-260 in the penton base and the FNPVYP motif at residues 11-16 in the fiber tail formed mutual interacting sites in the penton capsomer. The 2nd class consisted of phagotopes homologous to peptide sequences found in host cell membrane proteins involved in receptor or adhesion functions. One of the most abundant species corresponded to a conserved motif present in the .beta.-strand B of type III modules of human fibronectin. In addn., phages which were screened for their failure to bind to penton base RGD mutants were found to carry

consensus motifs to peptide sequences present in the RGD recognition site of human integrin .beta. subunits. The 3rd class comprised peptide motifs common to both viral and cellular proteins, suggesting that a mechanism of **ligand** exchange could occur during virus entry and uncoating and virus assembly and release.

L12 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:450825 CAPLUS
DOCUMENT NUMBER: 123:279199
TITLE: Highly heterogeneous fiber genes in the two closely related **adenovirus** genome types Ad35p and Ad34a
AUTHOR(S): Mei, Ya-Fang; Wadell, Goeran
CORPORATE SOURCE: Dep. Virol., Umea Univ., Umea, S-901 85, Swed.
SOURCE: Virology (1995), 206(1), 686-9
CODEN: VIRLAX; ISSN: 0042-6822
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two **adenovirus** isolates from urine, Ad35p (from a bone marrow recipient) and Ad34a (from a hemorrhagic cystitis patient), were compared regarding their fiber gene organization and hemagglutinating capacity. The fiber serves as the **ligand** between the **virus capsid** and the host cell receptor. The Ad35p fiber gene encoded a 323-amino-acid protein, and the Ad34a fiber gene a 325 amino acid protein. The two fibers manifested 62.4% overall amino acid sequence homol., the differences predominantly occurring within the knob region where sequence homol. was only 49.5%. The knob region of Ad34a was virtually identical to that of Ad11p which also causes hemorrhagic cystitis. Unlike all other known subgenus B **adenoviruses**, in the Ad35p fiber an asparagine constituted the C-terminus. Although both Ad34a and Ad35p viruses can hemagglutinate monkey erythrocytes, the hemagglutination inhibition test showed them to differ from each other in the epitopes expressed on the fibers.

L12 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:281669 CAPLUS
DOCUMENT NUMBER: 122:50899
TITLE: Mechanism of **adenovirus**-mediated endosome lysis: role of the intact **adenovirus** capsid structure
AUTHOR(S): Seth, Prem
CORPORATE SOURCE: Laboratory of Molecular Biology, Division of Cancer Biology and Diagnosis, Bethesda, MD, 20892, USA
SOURCE: Biochem. Biophys. Res. Commun. (1994), 205(2), 1318-24
CODEN: BBRCA9; ISSN: 0006-291X

DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Adenoviruses** have been previously shown to enhance the delivery of many **ligands** including proteins and plasmid DNAs to the cells. The key biochem. step during this process is the ability of **adenovirus** to disrupt (lyse) the endosome membrane releasing the co-internalized virus and the other **ligands** into the cytosol (Seth et al, 1986, In: **Adenovirus** attachment and entry into cells, pp 191-195, American Society for Microbiol., Washington, D.C.). To understand the role of the **adenovirus** proteins involved in the endosome lysis, it is further shown here that empty capsids of **adenovirus** also possess this membrane vesicle lytic activity; though the activity is about 5-times lower than the **adenovirus**. Incubation of **adenovirus** with low concn. of ionic detergent or brief exposure to 45.degree.C destroyed this lytic activity without affecting the **adenovirus** binding to cell surface receptor, suggesting the lytic activity of **adenovirus** to be of enzymic nature. However, exposing **adenovirus** to conditions that can disrupt **adenovirus** capsid structure such as heating at 65.degree.C, treating with 0.5% SDS, treating with different proteases, dialyzing against no glycerol buffer, treating with 6 M urea or with 10% pyridine, and sonication destroyed the **adenovirus**-assocd. lytic activity. Results suggest the requirement of an intact capsid structure for **adenovirus**-mediated lysis of the endosome.

L12 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:529541 CAPLUS
DOCUMENT NUMBER: 121:129541
TITLE: Characterization of the knob domain of the **adenovirus** type 5 fiber protein expressed in Escherichia coli
AUTHOR(S): Henry, Lynda J.; Xia, Di; Wilke, Marjorie E.; Deisenhofer, Johann; Gerard, Robert D.
CORPORATE SOURCE: Southwestern Med. Center, Univ. Texas, Dallas, TX, USA
SOURCE: J. Virol. (1994), 68(8), 5239-46
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **adenovirus** fiber protein is used for attachment of the virus to a specific receptor on the cell surface. Structurally, the protein consists of a long, thin shaft that protrudes from the vertex of the **virus capsid** and terminates in a globular domain termed the knob. To verify that the knob is the domain which interacts with the cellular receptor, the authors have cloned and expressed the knob from **adenovirus** type 5

together with a single repeat of the shaft in Escherichia coli. The protein was purified by conventional chromatog. and functionally characterized for its interaction with the **adenovirus** receptor. The recombinant knob domain bound about 4700 sites per HeLa cell with an affinity of 3 .times. 109 M-1 and blocked **adenovirus** infection of human cells. Antibodies raised against the knob also blocked virus infection. By gel filtration and X-ray diffraction anal. of protein crystals, the knob was shown to consist of a homotrimer of 21-kDa subunits. The results confirm that the trimeric knob is the **ligand** for attachment to the **adenovirus** receptor.

L12 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:317339 CAPLUS
DOCUMENT NUMBER: 120:317339
TITLE: Modification of a virus to redirect infectivity and enhance targeted delivery of polynucleotides to cells
INVENTOR(S): Wu, George Y.; Wu, Catherine H.
PATENT ASSIGNEE(S): The University of Connecticut, USA
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9406923	A1	19940331	WO 1993-US9034	19930923

W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1992-950453 19920924

AB Targeted polynucleotide delivery to cells is enhanced by coupling to a virus capable of disrupting cellular endosomes, a mol. complex which redirects viral specificity to the targeted cell and carries the polynucleotide to be delivered. Viruses useful in this invention, such as **adenovirus**, are generally those which possess exposed **capsid proteins** and which are capable of disrupting endosomal vesicles upon internalization by a receptor-bearing cell. The modified virus, which has linked to its surface a mol. complex comprised of a polynucleotide complexed with a carrier comprised of a cell-specific binding agent and a polynucleotide-binding agent, can be used in vivo, in vitro, or ex vivo to enhance the selective delivery of polynucleotides to target cells and gene expression. Enhanced expression (13.apprx.30-fold) of HBV surface antigen using wild type or dL312 of type 5

adenovirus with a conjugate comprised of human plasma-derived asialoorosomucoid (AsOR) with poly L-lysine (PL) was demonstrated.

[redacted]

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 12:29:25 ON 29 JUN 2001)

L13 77 S L11

[redacted]

L14 58 S L13 NOT L3

L15 30 DUP REM L14 (28 DUPLICATES REMOVED)

L15 ANSWER 1 OF 30 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2001-226694 [23] WPIDS

DOC. NO. CPI: C2001-067682

TITLE: Modified **adenoviral** fiber, useful for producing **adenoviral** particles for gene therapy, contains mutations that alter cell tropism.

DERWENT CLASS: B04 D16

INVENTOR(S): CUSACK, S; LEGRAND, V; LEISSNER, P; MEHTALI, M; VAN RAAIJ, M J

PATENT ASSIGNEE(S): (EMBL-N) EMBL EURO LAB MOLEKULARBIOLOGIE; (TRGE) TRANSGENE SA

COUNTRY COUNT: 22

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001016344	A1	20010308	(200123)*	FR	47

RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001016344	A1	WO 2000-FR2377	20000825

PRIORITY APPLN. INFO: FR 1999-10859 19990827

AN 2001-226694 [23] WPIDS

AB WO 200116344 A UPAB: 20010620

NOVELTY - A modified **adenoviral** fiber (A) containing at least one mutation in the region extending from the A sheet to the B sheet and including the AB loop, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(a) peptide fragments (I) containing the specified region of (A);

(b) DNA fragments (II), or expression vectors, encoding (A) or (I);

(c) cell lines containing, integrated into their genomes or maintained episomally, (II) under control of expression elements;

(d) **adenoviral** particles (AVP) lacking a natural fiber but containing (A), optionally also a **ligand** (L) that recognizes an anti-**ligand** (AL) other than the natural cellular receptor for the particles;

(e) a method for producing AVP of (d);

(f) method for producing AVP in which the genome lacks all or part of the fiber-encoding sequence; and

(g) composition containing AVP and a carrier.

USE - **Adenoviral** particles, or **adenoviruses**, that contain (A), but not the native fiber protein, optionally formulated with nucleic acid, are useful for gene therapy of diseases in humans and animals, e.g. cancer, a wide variety of inherited diseases and viral infections (including human immune deficiency virus (HIV)).

ADVANTAGE - Virus particles that contain (A), and optionally a selected **ligand**, are able to target cells that are not normally infected by **adenovirus**, but not the normal target cells. This reduces the quantity of virus needed to target selected cells, especially useful where cytotoxic genes are being delivered, to avoid damage to healthy, non-target cells.

Dwg.0/0

L15 ANSWER 2 OF 30 MEDLINE DUPLICATE 1

ACCESSION NUMBER:	2001200588 MEDLINE
DOCUMENT NUMBER:	21184699 PubMed ID: 11287567
TITLE:	Genetic targeting of an **adenovirus** vector via replacement of the fiber protein with the phage T4 fibritin.
AUTHOR:	Krasnykh V; Belousova N; Korokhov N; Mikheeva G; Curiel D T
CORPORATE SOURCE:	Division of Human Gene Therapy, Department of Medicine, and the Gene Therapy Center, University of Alabama at Birmingham, Birmingham, Alabama 35294, USA.
CONTRACT NUMBER:	N01 CO-97110 (NCI) R01 CA74242 (NCI) R01 CA83821 (NCI) R01 HL50255 (NHLBI)
SOURCE:	JOURNAL OF VIROLOGY, (2001 May) 75 (9) 4176-83. Journal code: KCV; 0113724. ISSN: 0022-538X.
PUB. COUNTRY:	United States Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals

ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010521
Last Updated on STN: 20010521
Entered PubMed: 20010405
Entered Medline: 20010517

AB The utility of **adenovirus** (**Ad**) vectors for gene therapy is restricted by their inability to selectively transduce disease-affected tissues. This limitation may be overcome by the derivation of vectors capable of interacting with receptors specifically expressed in the target tissue. Previous attempts to alter **Ad** tropism by genetic modification of the **Ad** fiber have had limited success due to structural conflicts between the fiber and the targeting **ligand**. Here we present a strategy to derive an **Ad** vector with enhanced targeting potential by a radical replacement of the fiber **protein** in the **Ad capsid** with a chimeric molecule containing a heterologous trimerization motif and a receptor-binding **ligand**. Our approach, which capitalized upon the overall structural similarity between the human **Ad** type 5 (Ad5) fiber and bacteriophage T4 fibritin proteins, has resulted in the generation of a genetically modified Ad5 incorporating chimeric fiber-fibritin proteins targeted to artificial receptor molecules. Gene transfer studies employing this novel viral vector have demonstrated its capacity to efficiently deliver a transgene payload to the target cells in a receptor-specific manner.

L15 ANSWER 3 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001086697 EMBASE
TITLE: **Adenovirus** type 5 viral particles pseudotyped with mutagenized fiber proteins show diminished infectivity of coxsackie B-**adenovirus** receptor-bearing cells.
AUTHOR: Jakubczak J.L.; Rollence M.L.; Stewart D.A.; Jafari J.D.; Von Seggern D.J.; Nemerow G.R.; Stevenson S.C.; Hallenbeck P.L.
CORPORATE SOURCE: S.C. Stevenson, Genetic Therapy, Inc./A Novartis Co., 9 West Watkins Mill Rd., Gaithersburg, MD 20878, United States. sue.stevenson@pharma.novartis.com
SOURCE: Journal of Virology, (2001) 75/6 (2972-2981).
Refs: 42
ISSN: 0022-538X CODEN: JOVIAM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A major limitation of **adenovirus** type 5 (Ad5)-based gene therapy, the inability to target therapeutic genes to selected cell

types, is attributable to the natural tropism of the virus for the widely expressed coxsackievirus-**adenovirus** receptor (CAR) protein. Modifications of the Ad5 fiber knob domain have been shown to alter the tropism of the virus. We have developed a novel system to rapidly evaluate the function of modified fiber proteins in their most relevant context, the **adenoviral** capsid. This transient transfection/infection system combines transfection of cells with plasmids that express high levels of the modified fiber protein and infection with Ad5..beta.gal..DELTA.F, an E1-, E3-, and fiber-deleted **adenoviral** vector encoding .beta.-galactosidase. We have used this system to test the **adenoviral** transduction efficiency mediated by a panel of fiber protein mutants that were proposed to influence CAR interaction. A series of amino acid modifications were incorporated via mutagenesis into the fiber expression plasmid, and the resulting fiber proteins were subsequently incorporated onto **adenoviral** particles. Mutations located in the fiber knob AB and CD loops demonstrated the greatest reduction in fiber-mediated gene transfer in HeLa cells. We also observed effects on transduction efficiency with mutations in the FG loop, indicating that the binding site may extend to the adjacent monomer in the fiber trimer and in the HI loop. These studies support the concept that modification of the fiber knob domain to diminish or ablate CAR interaction should result in a detargeted **adenoviral** vector that can be combined simultaneously with novel **ligands** for the development of a systemically administered, targeted **adenoviral** vector.

L15 ANSWER 4 OF 30 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
ACCESSION NUMBER: 2001:271566 BIOSIS
DOCUMENT NUMBER: PREV200100271566
TITLE: A simplified system for constructing recombinant **adenoviral** vectors containing heterologous peptides in the HI loop of their fiber knob.
AUTHOR(S): Mizuguchi, H. (1); Koizumi, N.; Hosono, T.; Utoguchi, N.; Watanabe, Y.; Kay, M. A.; Hayakawa, T.
CORPORATE SOURCE: (1) Division of Biological Chemistry and Biologicals, National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo, 158-8501 Japan
SOURCE: Gene Therapy, (May, 2001) Vol. 8, No. 9, pp. 730-735. print.
ISSN: 0969-7128.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The use of recombinant **adenovirus** (**Ad**) vectors containing genetically modified **capsid proteins** is an attractive strategy for achieving targeted gene transfer. The

HI loop of the fiber knob is a promising candidate location for the incorporation of foreign **ligands** for achieving this goal. However, the method of constructing an **Ad** vector containing a foreign **ligand** in the HI loop of the fiber knob has proved difficult. In this study, we developed a simple system to construct fiber-modified vectors. To do this, a vector plasmid containing a complete E1/E3-deleted **Ad** type 5 genome and a unique Csp45I and/or ClaI site between positions 32679 and 32680 of the **Ad** genome (residues threonine-546 and proline-547 of the fiber protein) was constructed. Oligonucleotides corresponding to the Arg-Gly-Asp (RGD) or Asn-Gly-Arg (NGR)-containing peptide motif (as a model) and containing a Csp45I and/or ClaI recognition site, were ligated into the Csp45I and/or ClaI-digested plasmid. The foreign transgene expression cassette was inserted into the E1 deletion site of the vector plasmid and the fiber-mutant **Ad** vector was produced by transfection of the Pac/I-digested plasmid into 293 cells. The virus containing the RGD or NGR peptide on the fiber knob was able to infect human glioma cells, which do not express coxsackievirus and **adenovirus** receptor (CAR), one of the **Ad** virus receptors, about 100-1000 times more efficient than the virus containing wild-type fiber. This suggested that the mutant virus mediated CAR-independent cell entry pathway. The simplicity of this method allows not only for easy construction of fiber-mutant **Ad** vectors, but also for screening of the peptides that target the vector to the desired cells and tissues.

L15 ANSWER 5 OF 30 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-376523 [32] WPIDS
DOC. NO. CPI: C2000-113925
TITLE: Recombinant parvoviral vectors with altered packaging, tropisms and immunogenic properties, useful in gene therapy protocols.
DERWENT CLASS: B04 D16
INVENTOR(S): RABINOWITZ, J E; SAMULSKI, R J; XIAO, W
PATENT ASSIGNEE(S): (UYNC-N) UNIV NORTH CAROLINA
COUNTRY COUNT: 86
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000028004	A1	20000518	(200032)*	EN	147

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

AU 2000019111 A 20000529 (200041)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000028004 A1		WO 1999-US26505	19991110
AU 2000019111 A		AU 2000-19111	19991110

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000019111 A	Based on	WO 200028004

PRIORITY APPLN. INFO: US 1999-123651 19990310; US 1998-107840 19981110

AN 2000-376523 [32] WPIDS

AB WO 200028004 A UPAB: 20000706

NOVELTY - A hybrid **virus** particle (I) comprising a parvovirus **capsid** and an AAV (adeno-associated **virus**) genome packaged within the **capsid**, is new. If the parvovirus capsid is an AAV capsid, the serotypes of the AAV capsid and the AAV genome are different.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated nucleic acid (II) encoding (I), comprising parvovirus cap (capsid) genes and AAV rep (repeat) genes (if the parvovirus cap genes are AAV cap genes, the serotype of the AAV cap genes and rep genes are different);

(2) a vector (III) comprising (II);

(3) a cell (IV) comprising (III);

(4) a method (V) of producing a hybrid virus particle, comprising providing a cell with AAV rep genes, parvovirus cap genes, an AAV genome and helper functions for generating a productive AAV infection (if the parvovirus cap genes are AAV cap genes, the serotypes of the AAV cap genes and the AAV genome are different);

(5) a hybrid virus particle (VI) produced by (V);

(6) a method (VI) of delivering a nucleic acid to a cell comprising introducing (I) into the cell;

(7) a method (VII) of administering a nucleic acid to a subject comprising administering (IV) and/or (I);

(8) a chimeric parvovirus capsid (VIII) comprise a cap region from an AAV **virus** and at least 1 **capsid** region from a B19 **virus**;

(9) an isolated nucleic acid (IX) encoding (VIII);

(10) a vector (X) comprising (IX); and

(11) a cell (XI) comprising (X).

ACTIVITY - None given.

MECHANISM OF ACTION - Nucleic acid vectors capable of delivering nucleic acids into cells.

No relevant data.

USE - (I) may be used in standard recombinant DNA protocols (e.g. gene therapy) as vectors for delivering nucleic acids to cells.

ADVANTAGE - The parvovirus packages larger than wild type AAV genomes and have altered antigenic properties and/or cellular tropisms (claimed).

Dwg.0/8

L15 ANSWER 6 OF 30 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2000-256653 [22] WPIDS

DOC. NO. CPI: C2000-078324

TITLE: Urokinase-type plasminogen activator receptor (UPAR)-targeted **adenovirus** vectors having modified hexon HRV5 and HI loops and modified fiber proteins useful for targeted gene therapy to treat cancer or restenosis.

DERWENT CLASS: B04 D16

INVENTOR(S): DEDIEU, J; LATTA, M; PERRICAUDET, M; VIGNE, E; YEH, P

PATENT ASSIGNEE(S): (AVET) AVENTIS PHARMA SA

COUNTRY COUNT: 80

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000012738	A1	20000309	(200022)*	EN	128
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AU BA BB BG BR CA CN CR CU CZ DM GD GE HR HU ID IL IN IS JP KP KR LC LK LR LT LV MG MK MN MX NO NZ PL RO RU SG SI SK SL TR TT UA US UZ VN YU ZA					
AU 9954393	A	20000321	(200031)		
EP 1108047	A1	20010620	(200135)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000012738	A1	WO 1999-IB1524	19990827
AU 9954393	A	AU 1999-54393	19990827
EP 1108047	A1	EP 1999-940416	19990827

WO 1999-IB1524 19990827

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9954393	A	Based on	WO 200012738
EP 1108047	A1	Based on	WO 200012738

PRIORITY APPLN. INFO: US 1998-98028 19980827
AN 2000-256653 [22] WPIDS
AB WO 200012738 A UPAB: 20000508
NOVELTY - An **adenovirus** from which at least a part of the hexon HRV5 or HI loop is replaced with a binding peptide, or targeting sequence, flanked by connecting amino acid spacers, to functionally display its binding specificity at the capsid surface is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a recombinant **adenovirus** vector where a binding peptide, or targeting sequence, is connected to the C-terminus of the fiber by a connecting spacer, or linker, so as to functionally display its binding specificity at the capsid surface;

(2) a method for modifying the cellular tropism of an **adenovirus** vector, comprising deleting a native amino acid sequence from a site in a **capsid protein** of the **adenovirus**, and inserting a targeting peptide sequence connected by first spacer at the N-terminus and a second spacer at the C-terminus of the targeting sequence, the targeting peptide is inserted in a deletion site selected from about 13 amino acids of HVR5 loop, corresponding to residues 269-281 of Ad5, and about 11 amino acids of fiber protein HI loop corresponding to residues 538-548 of Ad5;

(3) an **adenovirus** hexon or fiber protein where:

(a) the hexon protein comprises a deletion of about 13 amino acids from HVR5 loop corresponding to residues 269-281 of Ad5; or

(b) the fiber protein comprises a deletion of about 11 amino acids from HI loop corresponding to residues 538-548 of Ad5; and

(c) both have an insertion at the site of the deletion of a targeting peptide sequence connected by a first spacer at the N-terminus and a second spacer at the C-terminus of the targeting sequence;

(4) an **adenovirus** fiber protein comprising a linker peptide and a targeting peptide at its C-terminus;

(5) a medicine containing a targeted **adenovirus** vector of the novelty or (1), or produced by the method of (2);

(6) a pharmaceutical composition containing the medicine of (5) and a carrier; and

(7) a method for preferentially expressing a gene in a target cell, comprising contacting a population of cells containing the target cell with the novel **adenovirus**, the **adenovirus** of (1) or an **adenovirus** produced by the method of (2), the targeting sequence is a **ligand** epitope for a receptor on the target cell.

ACTIVITY - Cytostatic; Vasotropic.

MECHANISM OF ACTION - Gene Therapy.

USE - The **adenovirus** or recombinant **adenovirus** vector can be used to preferentially express a gene in a target cell, especially a cell that expresses a UPAR. The targeted **adenovirus** vector preferably comprises a heterologous gene encoding a gene for treatment of a tumor or restenosis. The targeted **adenovirus** vector is useful for gene therapy treatment of a disease, and for manufacturing a medicine for the treatment of a disease by gene therapy. (All claimed).

ADVANTAGE - The **adenoviruses** are tropism-modified without adversely impacting productivity of the vectors.

Dwg.0/14

L15 ANSWER 7 OF 30 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2000-099858 [09] WPIDS

CROSS REFERENCE: 2000-001282 [01]

DOC. NO. CPI: C2000-029183

TITLE: New methods for producing gene transfer vehicles, useful for targeted delivery of substances to cells.

DERWENT CLASS: B04 D16

INVENTOR(S): VAN ES, H

PATENT ASSIGNEE(S): (INTR-N) INTROGENE BV

COUNTRY COUNT: 25

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 972841	A1	20000119	(200009)*	EN	31

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 972841	A1	EP 1999-201592	19990520

PRIORITY APPLN. INFO: EP 1998-201678 19980520

AN 2000-099858 [09] WPIDS
CR 2000-001282 [01]
AB EP 972841 A UPAB: 20000218
NOVELTY - A method (A) for selecting at least one mutant protein (I) derived from a viral protein as a **ligand** capable of binding to a cell-surface receptor (III), is new and comprises displaying at least one (I) on the surface of a microorganism (II) expressing (I), where (II) is selected for its capacity to bind to (III).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a virus-like particle or gene delivery vehicle (IV) obtainable by (A); and

(2) a method (B) for selecting for a filamentous phage expressing a protein capable of binding to a **ligand**.

USE - (A) is used to select a protein which acts as a **ligand** and can bind to a cell-surface receptor (claimed). (B) is used to select a filamentous phage which can bind to a **ligand** or a cell expressing that **ligand** (claimed). Both these methods may be used to produce a virus-like particle or gene delivery vehicle which can be used for gene transfer (claimed). This is useful for the targeted delivery of substances to cells, such as compounds that kill tumor cells. The methods can be used to block the productive infection of cells in a human patient, and mutant envelope displaying phages that block a receptor can be used to treat pathogenic virus infections. The methods are therefore especially useful for human medicine.

ADVANTAGE - The gene transfer vehicles produced using (A) and (B) enable better application of gene transfer therapy than prior art methods. The prior art use of retroviruses are not highly effective because all known env variants have a broad infection spectrum in common. The new methods modify the infection spectrum of virus-like particles, producing increased specificity and efficiency.

Dwg.0/4

L15 ANSWER 8 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000400415 EMBASE
TITLE: Update on **adenovirus** and its vectors.
AUTHOR: Russell W.C.
CORPORATE SOURCE: W.C. Russell, School of Biology, University of St Andrews, Biomolecular Sci. Bldg., North Haugh, St Andrews, Fife KY16 9ST, United Kingdom. wcr@st-andrews.ac.uk
SOURCE: Journal of General Virology, (2000) 81/11 (2573-2604).
Refs: 407
ISSN: 0022-1317 CODEN: JGVIAY

COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
016 Cancer
022 Human Genetics
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English

L15 ANSWER 9 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001050932 EMBASE
TITLE: Exploring vascular heterogeneity for gene therapy targeting.
AUTHOR: Trepel M.; Arap W.; Pasqualini R.
CORPORATE SOURCE: M. Trepel, University of Freiburg Medical Ctr., Department of Hematology/Oncology, Hugstetter Strasse 55, D-79106 Freiburg, Germany
SOURCE: Gene Therapy, (2000) 7/24 (2059-2060).
Refs: 26
ISSN: 0969-7128 CODEN: GETHEC
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 004 Microbiology
022 Human Genetics
037 Drug Literature Index
LANGUAGE: English

L15 ANSWER 10 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001089480 EMBASE
TITLE: Targetable gene delivery vectors.
AUTHOR: Hallenbeck P.L.; Stevenson S.C.
SOURCE: Advances in Experimental Medicine and Biology, (2000) 465/- (37-46).
Refs: 49
ISSN: 0065-2598 CODEN: AEMBAP
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
016 Cancer
022 Human Genetics
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Adenoviral** vectors, which have targeting **ligands** for tumor cells on the capsid, no natural tropism, and carry a therapeutic payload should be constructed soon and tested in pre-clinical models. Nevertheless, there are still important considerations for the design and therapeutic use of targetable

vectors. Perhaps the single greatest challenge in the future, as it was in the past, will be finding **ligands** that have a higher apparent affinity for tumor and/or tumor endothelial cells then normal cells. However, the advent of many rapidly advancing technologies and information including the sequencing of the human genome, in vivo and in vitro phage display, rapid analysis of gene and protein expression in any context, and new cellular targets such as angiogenic endothelial cells, may provide many opportunities for the discovery of novel and useful **ligands**. In addition, the interests in targeting vectors are rapidly growing with new journals and meetings solely devoted to this subject increasing annually. Within the next 5 years, we should have meaningful clinical data on targetable vectors to reassess our progress.

L15 ANSWER 11 OF 30 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-444401 [37] WPIDS
DOC. NO. CPI: C1999-130938
TITLE: **Adenoviral** vectors with modified **capsid proteins** for improved infectious capabilities.
DERWENT CLASS: B04 D16
INVENTOR(S): ARMENTANO, D; O'RIORDAN, C R; ROMANCZUK, H
PATENT ASSIGNEE(S): (GENZ) GENZYME CORP
COUNTRY COUNT: 23
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9936545	A2	19990722	(199937)*	EN	59
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP US					
AU 9923219	A	19990802	(199954)		
EP 1044274	A2	20001018	(200053)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9936545	A2	WO 1999-US913	19990115
AU 9923219	A	AU 1999-23219	19990115
EP 1044274	A2	EP 1999-903122	19990115
		WO 1999-US913	19990115

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 9923219 A Based on WO 9936545
EP 1044274 A2 Based on WO 9936545

PRIORITY APPLN. INFO: US 1998-71674 19980116
AN 1999-444401 [37] WPIDS
AB WO 9936545 A UPAB: 19990914
NOVELTY - An **adenoviral capsid protein** comprising a heterologous **ligand**, where the **ligand** facilitates binding of the **adenovirus** to a target cell, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a heterologous **ligand** having a sequence (Ad17 RGD) and (sss.17);

(2) an oligonucleotide encoding a **ligand** as above;

(3) an **adenoviral** vector which comprises a transgene operably linked to expression control sequences and further comprises an **adenoviral capsid protein** as above; and

(4) a complex comprising a heterologous **ligand** as above and a cellular receptor which binds to the **ligand**:

GPARGDSSV (Ad17RGD)

SPQLASPYSHPR (sss 17)

ACTIVITY - Gene Transfer.

MECHANISM OF ACTION - Gene Delivery Vehicle; Vector.

USE - The **adenoviral** vector is used to transfer a transgene to a target cell. The heterologous **ligand** in the **adenoviral capsid protein** (especially a fiber or hexon protein or protein IX) facilitates binding of the vector to the target cell (all claimed). In particular, the **adenoviral** vector can be used to transfer the human cystic fibrosis transmembrane conductance regulator protein gene to the respiratory epithelium of test animals.

ADVANTAGE - The modified **adenoviral capsid proteins** improve and/or alter the infectious capability of the vector. Balb/c mice were instilled with 5 x 108 I.U. of each **adenoviral** vector. At 3 days post-instillation, mice were sacrificed to determine beta -gal expression in the lungs by X-gal staining and AMPGD analysis. The results were expressed in relative light units per microgram protein (RLU/ mu g). Substitution of a sss.17 peptide in the hexon loop 1 of an **adenoviral** vector increases transduction efficiency 2.4-fold in comparison to a wild-type vector (Ad2/ beta -gal4). Substitution with the Ad17RGD peptide in hexon loop 1 increases transduction efficiency 2.5-fold.

DESCRIPTION OF DRAWING(S) - Transduction of mouse lung cells by **adenoviral** vectors with modified hexon proteins.

Dwg.0/9

L15 ANSWER 12 OF 30 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-025491 [03] WPIDS
CROSS REFERENCE: 2000-001283 [01]
DOC. NO. CPI: C2000-006530
TITLE: New gene therapy vectors, useful for treating balloon angioplasty patients.
DERWENT CLASS: B04 D16
INVENTOR(S): HAVENGA, M; VAN ES, H; VERLINDEN, S
PATENT ASSIGNEE(S): (INTR-N) INTROGENE BV
COUNTRY COUNT: 25
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 960942	A2	19991201	(200003)*	EN	50

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 960942	A2	EP 1999-201593	19990520

PRIORITY APPLN. INFO: EP 1998-201693 19980520
AN 2000-025491 [03] WPIDS
CR 2000-001283 [01]
AB EP 960942 A UPAB: 20000118
NOVELTY - A virus-like particle or gene delivery vehicle (I) is new and expresses a **ligand** capable of binding to a human amino acid transporter.

USE - (I) is used to deliver genes to human cells (claimed) or primate cells that express the hCAT1 amino acid transporter, such as endothelial, hematopoietic or smooth muscle cells, as part of a gene therapy regime. The vectors are especially useful for providing local applications of **adenoviral** vector to patients with restenosis following balloon angioplasty, where smooth muscle cells need to be transduced with ceNOS cDNA, for example. (I) may also be used to pseudotype recombinant type C retrovirus including murine leukemia retroviruses and lentiviruses. In addition (I) may be used in functional genomics where transduction of as many cell types as possible is required.

ADVANTAGE - The new gene delivery vehicles transduce DNA more efficiently and specifically into tissues that are hard to transform, such as endothelial cells or smooth muscle cells as compared to a wildtype **adenoviral** vector. This increased specificity results in lower multiplicities of infection which can

occur with prior art vectors, so preventing tissue toxicity. In addition the new vectors allow DNA to be transduced into cells that are in low abundance in cell mixtures and tissues, which increases their efficiency for use as gene therapy vehicles. The alteration of the **ligand** on the viral envelope increases the potential host cell range of these vehicles.
Dwg.0/22

L15 ANSWER 13 OF 30 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-001283 [01] WPIDS
CROSS REFERENCE: 2000-025491 [03]
DOC. NO. CPI: C2000-000389
TITLE: New virus-like particle or gene delivery vehicle, useful for gene therapy.
DERWENT CLASS: B04 D16
INVENTOR(S): HAVENGA, M; VAN ES, H; VERLINDEN, S
PATENT ASSIGNEE(S): (INTR-N) INTROGENE BV
COUNTRY COUNT: 30
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 959136	A1	19991124	(200001)*	EN	65
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
WO 9960147	A2	19991125	(200003)	EN	
W: AU CA JP MX NZ					
AU 9940640	A	19991206	(200019)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 959136	A1	EP 1998-201693	19980520
WO 9960147	A2	WO 1999-NL310	19990520
AU 9940640	A	AU 1999-40640	19990520

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9940640	A	Based on	WO 9960147

PRIORITY APPLN. INFO: EP 1998-201693 19980520
AN 2000-001283 [01] WPIDS
CR 2000-025491 [03]
AB EP 959136 A UPAB: 20000419
NOVELTY - A virus-like particle or gene delivery vehicle is new and

comprises a **ligand** capable of binding to a human amino acid transporter.

USE - The method is useful for the target delivery of substances to cells e.g. gene therapy. An hCAT1 targeted **adenovirus** is useful for local applications of **adenoviral** vector e.g. in patients with restenosis following balloon angioplasty where smooth muscle cells need to be transduced with an **adenoviral** vector carrying the CeNOS cDNA.

ADVANTAGE - More efficient transduction of tissues can be carried out therefore resulting in lower multiplicity's of infections that can be used and therefore less vector associated toxicity to the tissues surrounding the target cells.

Dwg.0/17

L15 ANSWER 14 OF 30 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-001282 [01] WPIDS
DOC. NO. CPI: C2000-000388
TITLE: Selecting mutant **ligands** fro cell surface receptors, allowing improved delivery of substances to cells.
DERWENT CLASS: B04 D16
INVENTOR(S): VAN ES, H
PATENT ASSIGNEE(S): (INTR-N) INTROGENE BV
COUNTRY COUNT: 30
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 959135	A1	19991124	(200001)*	EN	30
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
WO 9960148	A2	19991125	(200003)	EN	
W: AU CA JP MX NZ					
AU 9940641	A	19991206	(200019)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 959135	A1	EP 1998-201678	19980520
WO 9960148	A2	WO 1999-NL311	19990520
AU 9940641	A	AU 1999-40641	19990520

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9940641	A	Based on	WO 9960148

PRIORITY APPLN. INFO: EP 1998-201678 19980520
AN 2000-001282 [01] WPIDS
AB EP 959135 A UPAB: 20000218
NOVELTY - A method for selecting at least one mutant protein derived from a viral protein as a **ligand** capable of binding to a cell-surface receptor, comprising displaying at least one mutant protein on the surface of a microorganism expressing it, and further comprising selecting the mutant microorganism for its capacity to bind to the receptor.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a virus-like particle or gene delivery vehicle obtained by the method; and

(2) a method for selecting a filamentous phage expressing a protein capable of binding to a **ligand**, comprising:

(i) constructing a phage library; and

(ii) enriching the library for phage which have the desired binding characteristics by at least one round of phage selection for their capacity to bind to a synthetic peptide derived from the **ligand**.

USE - The virus-like particles and gene delivery vehicles obtained by the novel method are used as gene-transfer vehicles. The novel methods allows the targeted delivery of substances to cells, allowing specific treatment of cells with compounds which will act in the target cell, for possible use in gene therapy techniques.

ADVANTAGE - Prior gene therapy methods using retroviruses have been hampered by broad infection spectrums of the retrovirus, this method allows the targeted delivery of substances which will reduce the infection spectrum.

Dwg.0/4

L15 ANSWER 15 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999187221 EMBASE
TITLE: RGD inclusion in the hexon monomer provides **adenovirus** type 5-based vectors with a fiber knob-independent pathway for infection.
AUTHOR: Vigne E.; Mahfouz I.; Dedieu J.-F.; Brie A.; Perricaudet M.; Yeh P.
CORPORATE SOURCE: P. Yeh, CNRS-IGR-Rhone Poulenc Rorer UMR1582, Institut Gustave Roussy, Rue Camille Desmoulins, 94805 Villejuif Cedex, France. pyeh@igr.fr
SOURCE: Journal of Virology, (1999) 73/6 (5156-5161).
Refs: 26
ISSN: 0022-538X CODEN: JOVIAM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology

LANGUAGE: English
SUMMARY LANGUAGE: English
AB Hypervariable region 5 (HVR5) is a hydrophilic, serotypically nonconserved loop of the hexon monomer which extrudes from the **adenovirus** (**Ad**) capsid. We have replaced the HVR5 sequence of Ad5 with that of heterologous peptides and studied their effects on virus viability and peptide accessibility. A poliovirus model epitope was first inserted in a series of nine 'isogenic' viruses that differed in their flanking spacers. Whereas virus productivity was not profoundly altered by any of these modifications, immunoprecipitation experiments under nondenaturing conditions demonstrated that epitope recognition by its cognate monoclonal antibody (C3 MAb) was strongly linker dependent and correlated perfectly with the ability of C3 MAb to inhibit transgene delivery and expression. An .alpha.(v)-specific **ligand** (DCRGDCF) was then inserted in a suitable linker context to investigate whether hexon-modified capsids would enhance the transduction of cells displaying limiting amounts of the virus attachment receptors. Interestingly, although hexon has never been implicated in **Ad** entry, the modified virus significantly increased the transduction of human vascular smooth muscle cells in vitro. Competition experiments with 293 cells saturated with recombinant knob further indicated that the hexon-modified virus could use an additional, knob-independent pathway for entry. We concluded that genetic engineering of the Ad5 hexon monomer constitutes a novel and feasible approach to equip the virus with additional targeting **ligands**.

L15 ANSWER 16 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999406533 EMBASE
TITLE: Modification of an **adenoviral** vector with biologically selected peptides: A novel strategy for gene delivery to cells of choice.
AUTHOR: Romanczuk H.; Galer C.E.; Zabner J.; Barsomian G.; Wadsworth S.C.; O'Riordan C.R.
CORPORATE SOURCE: Dr. H. Romanczuk, Genzyme Corporation, 31 New York Avenue, Framingham, MA 01701, United States. hromanczuk@genzyme.com
SOURCE: Human Gene Therapy, (1 Nov 1999) 10/16 (2615-2626). Refs: 44
ISSN: 1043-0342 CODEN: HGTHE3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Recombinant **adenoviruses** are currently being used as vectors for gene delivery to a wide variety of cells and tissues.

Although generally efficacious for gene transfer in vitro, improvement in the efficiency of vector delivery in vivo may aid several gene therapy applications. One major obstacle is the lack of high-affinity viral receptors on the surface of certain cells that are targets for gene therapy. In principle, incorporation of avid, cell-specific **ligands** into the virion could markedly improve vector entry into the desired tissues. We have developed a strategy for addressing this issue in the lung by biopanning differentiated, ciliated airway epithelial cells against a phage display library. The peptide with the most effective binding was coupled to the surface of an **adenovirus** using bifunctional polyethylene glycol (PEG) molecules. The chemically modified **adenoviral** vector was able to effect gene transfer to well-differentiated human airway epithelial cells by an alternative pathway dependent on the incorporated peptide. Coupling of PEG to the surface of the virus also served to partially protect the virus from neutralizing antibodies in vitro. These experiments will aid in the design of improved **adenoviral** vectors with the capacity for more specific and efficient delivery of therapeutic genes to desired target tissues.

L15 ANSWER 17 OF 30 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999098977 MEDLINE
DOCUMENT NUMBER: 99098977 PubMed ID: 9882291
TITLE: Fiberless recombinant **adenoviruses**: virus maturation and infectivity in the absence of fiber.
AUTHOR: Legrand V; Spehner D; Schlesinger Y; Settelen N; Pavirani A; Mehtali M
CORPORATE SOURCE: Transgene S.A., 67000 Strasbourg, France.
SOURCE: JOURNAL OF VIROLOGY, (1999 Feb) 73 (2) 907-19.
Journal code: KCV; 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990301
Last Updated on STN: 20000824
Entered Medline: 19990218

AB In vivo targeting of therapeutic genes to specific tissues has become a major issue in gene therapy, in particular when recombinant **adenovirus** vectors are used. Restriction of the viral tropism to selected cell types requires the abrogation of the interaction between the viral fiber and its natural cellular receptors and the introduction of a new binding specificity into the virion. In this context, fiberless **adenoviruses** are attractive vectors, since they may be used as substrates for the insertion of a new **ligand** in other **capsid**

proteins. In this study, we confirm by using cloned full-length **adenovirus** genomes with the fiber gene deleted that efficient virus particle formation can occur in the absence of fiber. As expected, the infectivity of such fiberless viruses was severely reduced, but it could be only partially restored when the viruses were produced in cells stably providing the fiber in trans. Although incorporation of penton base into the fiberless particles was normal and binding of the particles to the cellular integrins was functional, several pieces of experimental evidence suggest that later steps in the cell entry process are impaired in correlation with an incorrect maturation of several structural proteins of the fiberless particles. These observations support the hypothesis that the fiber protein may have additional biological functions besides its role in cell binding. Together with the fiber complementation cells, such fiberless vectors constitute unique tools to investigate the role of the fiber in virus assembly, maturation, and cell entry and to explore the possibility of deriving gene transfer vectors with novel target specificities.

L15 ANSWER 18 OF 30 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1998-520825 [44] WPIDS
DOC. NO. CPI: C1998-156366
TITLE: New tropism modified **adenoviral** vectors - comprise antibody that binds **adenoviral capsid protein, ligand** that binds a receptor and nucleic acid encoding therapeutic gene product.
DERWENT CLASS: B04 D16
INVENTOR(S): BAIRD, A; CURIEL, D T; DOUGLAS, J T; PIERCE, G F; ROGERS, B E; SOSNOWSKI, B A; SONOWSKI, B
PATENT ASSIGNEE(S): (BAIR-I) BAIRD A; (CURI-I) CURIEL D T; (DOUG-I) DOUGLAS J T; (PIER-I) PIERCE G F; (ROGE-I) ROGERS B E; (SOSN-I) SOSNOWSKI B A; (SELE-N) SELECTIVE GENETICS INC; (UABR-N) UAB RES FOUND
COUNTRY COUNT: 80
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9840508	A1	19980917	(199844)*	EN	204
RW: AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW					
AU 9864629	A	19980929	(199906)		
EP 973926	A1	20000126	(200010)	EN	

R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9840508	A1	WO 1998-US4964	19980313
AU 9864629	A	AU 1998-64629	19980313
EP 973926	A1	EP 1998-910375	19980313
		WO 1998-US4964	19980313

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9864629	A	Based on	WO 9840508
EP 973926	A1	Based on	WO 9840508

PRIORITY APPLN. INFO: US 1997-65265 19971110; US 1997-40782 19970314

AN 1998-520825 [44] WPIDS

AB WO 9840508 A UPAB: 19981104

The following are claimed: (1) a tropism-modified **adenoviral** vector (TMAV) system that specifically targets cells expressing a preselected receptor, comprising: (a) an antibody or fragment that binds an **adenoviral capsid protein**; (b) a targeting **ligand** that binds the preselected receptor, and (c) an **Adenovirus** (**Ad**) containing a nucleic acid molecule (NAM) that encodes a therapeutic gene product (TGP) under the control of a promoter; where the **ligand** is conjugated to the antibody or fragment and where the antibody or fragment is bound to the **Ad**, and (2) a therapeutical composition comprising a physiologically acceptable buffer and a TMAV presenting a **ligand** on its surface, where the vector includes a NAM encoding a TGP under the control of a promoter.

USE - The products can be used to replace or repair defective, improperly regulated, or nonfunctional genes. They can be used to stimulate wound healing, tissue repair, connective tissue growth, angiogenesis, the amelioration of ischemia, to treat, interfere with or block a disease process such as hyperproliferation of cells, tumour growth, or metastasis. The products can also be used to treat angiogenesis-dependent diseases, e.g. angiofibroma, arteriovenous malformations, arthritis, atherosclerotic plaques, corneal graft neovascularisation, delayed wound healing, diabetic retinopathy, granulations due to burns, haemangionas, haemophilic joints, hypertrophic scars, neovascular glaucoma, nonunion fractures, Osler-Weber syndrome, psoriasis, pyogenic granuloma, retrolental

fibroplasia, scleroderma, trachoma, or vascular adhesions.

ADVANTAGE - Altering the tropism of an Ad significantly enhances targeting efficiency and nuclear trafficking of the Ad vector well above that seen when the vector retains its native Ad tropism, and also increases the infectability of Ad in various cells.

Dwg.0/21

L15 ANSWER 19 OF 30 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 97296288 MEDLINE

DOCUMENT NUMBER: 97296288 PubMed ID: 9151872

TITLE: Selective targeting of human cells by a chimeric **adenovirus** vector containing a modified fiber protein.

AUTHOR: Stevenson S C; Rollence M; Marshall-Neff J; McClelland A

CORPORATE SOURCE: Department of Molecular and Cell Biology, Genetic Therapy, Inc., Gaithersburg, Maryland 20878, USA.

SOURCE: JOURNAL OF VIROLOGY, (1997 Jun) 71 (6) 4782-90. Journal code: KCV; 0113724. ISSN: 0022-538X.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199706

ENTRY DATE: Entered STN: 19970620
Last Updated on STN: 19970620
Entered Medline: 19970609

AB The **adenovirus** fiber protein is responsible for attachment of the virion to unidentified cell surface receptors. There are at least two distinct **adenovirus** fiber receptors which interact with the group B (Ad3) and group C (Ad5) **adenoviruses**. We have previously shown by using expressed **adenovirus** fiber proteins that it is possible to change the specificity of the fiber protein by exchanging the head domain with another serotype which recognizes a different receptor (S. C. Stevenson et al., J. Virol. 69:2850-2857, 1995). A chimeric fiber cDNA containing the Ad3 fiber head domain fused to the Ad5 fiber tail and shaft was incorporated into the genome of an **adenovirus** vector with E1 and E3 deleted encoding beta-galactosidase to generate Av9LacZ4, an **adenovirus** particle which contains a chimeric fiber protein. Western blot analysis of the chimeric fiber vector confirmed expression of the chimeric fiber protein and its association with the **adenovirus capsid**. Transduction experiments with fiber **protein** competitors demonstrated the altered receptor tropism of the chimeric fiber vector compared to that of the parental Av1LacZ4 vector. Transduction of a panel of human cell

lines with the chimeric and parental vectors provided evidence for a different cellular distribution of the Ad5 and Ad3 receptors. Three cell lines (THP-1, MRC-5, and FaDu) were more efficiently transduced by the vector containing the Ad3 fiber head than by the Ad5 fiber vector. In contrast, human coronary artery endothelial cells were transduced more readily with the vector containing the Ad5 fiber than with the chimeric fiber vector. HeLa and human umbilical vein endothelial cells were transduced at equivalent levels compared with human diploid fibroblasts, which were refractory to transduction with both vectors. These results provide evidence for the differential expression of the Ad5 and Ad3 receptors on human cell lines derived from clinically relevant target tissues. Furthermore, we show that exchange of the fiber head domain is a viable approach to the production of **adenovirus** vectors with cell-type-selective transduction properties. It may be possible to extend this approach to the use of **ligands** for a range of different cellular receptors in order to target gene transfer to specific cell types at the level of transduction.

L15 ANSWER 20 OF 30 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 97:548077 SCISEARCH
THE GENUINE ARTICLE: XL048
TITLE: Targeted **adenoviral** vectors for cancer gene therapy (Review)
AUTHOR: Douglas J T; Curiel D T (Reprint)
CORPORATE SOURCE: UNIV ALABAMA, GENE THERAPY PROGRAM, 1824 6TH AVE S, WTI 620, BIRMINGHAM, AL 35294 (Reprint); UNIV ALABAMA, GENE THERAPY PROGRAM, BIRMINGHAM, AL 35294
COUNTRY OF AUTHOR: USA
SOURCE: INTERNATIONAL JOURNAL OF ONCOLOGY, (AUG 1997) Vol. 11, No. 2, pp. 341-348.
Publisher: INT JOURNAL ONCOLOGY, C/O PROFESSOR D A SPANDIDOS, EDITORIAL OFFICE, 1, S MERKOURI ST, ATHENS 116 35, GREECE.
ISSN: 1019-6439.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 66

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In order to realise the full potential of gene therapy as a rational approach to the treatment of cancer, it will be necessary to achieve delivery of the therapeutic gene selectively to target tumour cells. Such cancer cell-specific gene delivery is mandated in the context of locoregional or compartmentalised carcinomas, and is also an absolute requirement for the treatment of disseminated disease. Moreover, underlying any cancer gene therapy approach is the need to achieve a high level of efficiency of gene transfer to

the target cells. Of the existing viral and nonviral gene delivery vehicles, the **adenoviral** vector uniquely fulfils two requirements of an intravenously administered vector for cancer gene therapy: systemic stability and the ability to accomplish efficient transduction of cancer cells. However, it is necessary to modify native **adenoviral** tropism in order to achieve selective transduction of target tumour cells. A number of strategies have been developed for this purpose, involving genetic or immunological modifications to either of two **adenoviral capsid proteins**, the fibre and penton base. These strategies are designed to generate a targetable, injectable vector which would represent a major advance in the field of cancer gene therapy.

L15 ANSWER 21 OF 30 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 96323159 MEDLINE
DOCUMENT NUMBER: 96323159 PubMed ID: 8709265
TITLE: Transient subversion of CD40 **ligand** function diminishes immune responses to **adenovirus** vectors in mouse liver and lung tissues.
AUTHOR: Yang Y; Su Q; Grewal I S; Schilz R; Flavell R A; Wilson J M
CORPORATE SOURCE: Institute for Human Gene Therapy, University of Pennsylvania Health System, Philadelphia, USA.
SOURCE: JOURNAL OF VIROLOGY, (1996 Sep) 70 (9) 6370-7. Journal code: KCV; 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960919
Last Updated on STN: 19960919
Entered Medline: 19960910

AB First-generation **adenovirus** vectors will have limited application in gene therapy for chronic diseases because of destructive host immune responses. Important immune effectors include CD8+ T cells, which mediate target cell destruction and ablate transgene expression, and B cells, which produce neutralizing antibodies that block effective readministration of vector. Previous studies indicated that activation of CD4+ T cells by **virus capsid proteins** is necessary for full realization of effector function of CD8+ T cells and B cells. In this paper, we present a strategy for preventing CD4+ T-cell activation by an **adenovirus** vector delivered to mouse liver and lung tissues which is based on interfering with T-cell priming via CD40 **ligand**-CD40 interactions. **Adenovirus** transgene expression was stabilized in mice genetically deficient in CD40

ligand (CD40L), and neutralizing antibody to **adenovirus** did not develop, allowing efficient readministration of vector. A transient blockade of T-cell activation with an antibody to CD40L infused into the animal at the time of **adenovirus** vector-mediated gene transfer led to stabilization of transgene expression and diminished production of neutralizing antibody, allowing readministration of vector. In vitro T-cell assays suggested that a block in the primary activation of CD4+ T cells was responsible for the lack of B-cell- and cytotoxic-T-cell-dependent responses. This suggests a strategy for improving the potential of **adenovirus** vectors based on administration of an antibody to CD40L at the time of vector administration.

L15 ANSWER 22 OF 30 MEDLINE DUPLICATE 6

ACCESSION NUMBER: 96183852 MEDLINE
DOCUMENT NUMBER: 96183852 PubMed ID: 8642632
TITLE: **Adenovirus** type 5 and 7 capsid chimera: fiber replacement alters receptor tropism without affecting primary immune neutralization epitopes.
AUTHOR: Gall J; Kass-Eisler A; Leinwand L; Falck-Pedersen E
CORPORATE SOURCE: Department of Microbiology, W.R. Hearst Research Foundation, Cornell University College of Medicine, New York, New York 10021, USA.
CONTRACT NUMBER: 5P01 HL51746 (NHLBI)
RO1GM29090 (NIGMS)
SOURCE: JOURNAL OF VIROLOGY, (1996 Apr) 70 (4) 2116-23.
Journal code: KCV; 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960726
Last Updated on STN: 20000907
Entered Medline: 19960718

AB The efficient uptake of **adenovirus** into a target cell is a function of **adenovirus capsid proteins** and their interaction with the host cell. The **capsid protein** fiber mediates high-affinity attachment of **adenovirus** to the target cell. Although the cellular receptor(s) for **adenovirus** is unknown, evidence indicates that a single receptor does not function as the attachment site for each of the 49 different serotypes of **adenovirus**. Sequence variation of the fiber **ligand**, particularly in the C-terminal knob domain, is associated with serotype-specific binding specificity. Additionally, this domain of fiber functions as a major serotype determinant. Fiber involvement in cell targeting and its

function as a target of the host immune response make the fiber gene an attractive target for manipulation, both from the perspective of **adenovirus** biology and from the perspective of using **adenovirus** vectors for gene transfer experiments. We have constructed a defective chimeric **adenovirus** type 5 (Ad5) reporter virus by replacing the Ad5 fiber gene with the fiber gene from Ad7A. Using the chloramphenicol acetyltransferase reporter gene, we have characterized this virus with respect to infectivity both in vitro and in vivo. We have also characterized the role of antifiber antibody in the host neutralizing immune response to **adenovirus** infection. Our studies demonstrate that exchange of fiber is a strategy that will be useful in characterizing receptor tropism for different serotypes of **adenovirus**. Additionally, the neutralizing immune response to Ad5 and Ad7 does not differentiate between two viruses that differ only in their fiber proteins. Therefore, following a primary **adenovirus** inoculation, antibodies generated against fiber do not constitute a significant fraction of the neutralizing antibody population.

L15 ANSWER 23 OF 30 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 97081754 MEDLINE
DOCUMENT NUMBER: 97081754 PubMed ID: 8922997
TITLE: Immunology of gene therapy with **adenoviral** vectors in mouse skeletal muscle.
AUTHOR: Yang Y; Haecker S E; Su Q; Wilson J M
CORPORATE SOURCE: Institute for Human Gene Therapy, University of Pennsylvania Medical Center, Philadelphia 19104, USA.
SOURCE: HUMAN MOLECULAR GENETICS, (1996 Nov) 5 (11) 1703-12. Journal code: BRC; 9208958. ISSN: 0964-6906.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970321
Last Updated on STN: 19970321
Entered Medline: 19970311

AB Skeletal muscle is an attractive target for somatic gene transfer of both acquired and inherited disorders. Direct injection of **adenoviral** vectors in the skeletal muscle leads to recombinant gene expression in a large number of muscle fibers. Transgene expression has been transient in most organs and associated with substantial inflammation when experiments are performed in adult immune competent mice. In this report, we utilize a variety of in vivo and in vitro models of T and B cell function to characterize the nature of the immune response to **adenoviral** vectors injected into murine skeletal muscle. Cellular immunity dependent on CD4+ and CD8+ T cells contributes to the loss of

recombinant gene expression and the development of localized inflammation. Antigen specific activation of T cells occurs to both viral proteins and the reporter gene beta-galactosidase. Systemic levels of neutralizing antibody to the **capsid proteins** of the vector are also generated. Destructive immune responses responsible for loss of transgene expression are largely directed against beta-galactosidase in that transgene expression was stable when beta-galactosidase was eliminated as a neoantigen in mice transgenic for lacZ. A strategy to prevent the cellular and humoral immunity to this therapy was developed based on transiently ablating CD4+ T cell activation at the time of vector delivery. Encouraging results were obtained when vector was administered with one of several immune modulating agents including cyclophosphamide, mAb to CD4+ cells, and mAb to CD40 **ligand** . These studies indicate that cellular and humoral immune responses are elicited in the context of gene therapy directed to skeletal muscle with **adenoviral** vectors. Transient ablation of CD4+ T cell activation prevents the effects responses of the CD8+ T and B cells.

L15 ANSWER 24 OF 30 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1995:532869 BIOSIS
DOCUMENT NUMBER: PREV199598547169
TITLE: Protein **ligands** of the human **adenovirus** type 2 outer capsid identified by biopanning of a phage-displayed peptide library on separate domains of wild-type and mutant penton capsomers.
AUTHOR(S): Hong, Saw See; Boulanger, Pierre (1)
CORPORATE SOURCE: (1) Lab. Virol. Pathogenese Moleculaires, Inst. Biol., Fac. Med., 34060 Montpellier France
SOURCE: EMBO (European Molecular Biology Organization) Journal, (1995) Vol. 14, No. 19, pp. 4717-4727. ISSN: 0261-4189.
DOCUMENT TYPE: Article
LANGUAGE: English
AB A filamentous phage-displayed random hexapeptide library was screened on the **adenovirus** type 2 (Ad2) penton capsomer and its separate domains, penton base, full-length fiber, fiber shaft and fiber knob. Affinity supports were designed to immobilize the penton ligate with a preferred orientation, via immunoadsorption to pre-coated antibody. Three classes of phagotopes were distinguished in the eluates from the penton and fiber domains. (i) The first class represented peptide sequences identified in certain Ad2 **capsid proteins**, **protein** IIIa, **protein** pVIII, penton base and penton fiber. Data from specific **ligand** elution of phages bound to fiber and penton base wild-types and mutants suggested that the region

overlapping the RLSNLLG motif at residues 254-260 in the penton base and the FNPVYP motif at residues 11-16 in the fiber tail formed mutual interacting sites in the penton capsomer. (ii) The second class consisted of phagotopes homologous to peptide sequences found in host cell membrane proteins involved in receptor or adhesion functions. One of the most abundant species corresponded to a conserved motif present in the beta-strand B of type III modules of human fibronectin. In addition, phages which were screened for their failure to bind to penton base RGD mutants were found to carry consensus motifs to peptide sequences present in the RGD recognition site of human integrin beta subunits. (iii) The third class comprised peptide motifs common to both viral and cellular proteins, suggesting that a mechanism of **ligand** exchange could occur during virus entry and uncoating, and virus assembly and release.

L15 ANSWER 25 OF 30 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 96030777 MEDLINE
DOCUMENT NUMBER: 96030777 PubMed ID: 7588601
TITLE: Protein **ligands** of the human **adenovirus** type 2 outer capsid identified by biopanning of a phage-displayed peptide library on separate domains of wild-type and mutant penton capsomers.
AUTHOR: Hong S S; Boulanger P
CORPORATE SOURCE: Laboratoire de Virologie et Pathogenese Moleculaires (CNRS URA 1487), Institut de Biologie, Faculte de Medecine, Montpellier, France.
SOURCE: EMBO JOURNAL, (1995 Oct 2) 14 (19) 4714-27.
Journal code: EMB; 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951128

AB A filamentous phage-displayed random hexapeptide library was screened on the **adenovirus** type 2 (Ad2) penton capsomer and its separate domains, penton base, full-length fiber, fiber shaft and fiber knob. Affinity supports were designed to immobilize the penton ligate with a preferred orientation, via immuno-adsorption to pre-coated antibody. Three classes of phagotopes were distinguished in the eluates from the penton and fiber domains. (i) The first class represented peptide sequences identified in certain Ad2 **capsid proteins**, **protein** IIIa, **protein** pVIII, penton base and penton fiber. Data from specific **ligand** elution of phages

bound to fiber and penton base wild-types and mutants suggested that the region overlapping the RLSNLLG motif at residues 254-260 in the penton base and the FNPVYP motif at residues 11-16 in the fiber tail formed mutual interacting sites in the penton capsomer. (ii) The second class consisted of phagotopes homologous to peptide sequences found in host cell membrane proteins involved in receptor or adhesion functions. One of the most abundant species corresponded to a conserved motif present in the beta-strand B of type III modules of human fibronectin. In addition, phages which were screened for their failure to bind to penton base RGD mutants were found to carry consensus motifs to peptide sequences present in the RGD recognition site of human integrin beta subunits. (iii) The third class comprised peptide motifs common to both viral and cellular proteins, suggesting that a mechanism of **ligand** exchange could occur during virus entry and uncoating, and virus assembly and release.

L15 ANSWER 26 OF 30 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 95133210 MEDLINE
DOCUMENT NUMBER: 95133210 PubMed ID: 7831826
TITLE: Highly heterogeneous fiber genes in the two closely related **adenovirus** genome types Ad35p and Ad34a.
AUTHOR: Mei Y F; Wadell G
CORPORATE SOURCE: Department of Virology, Umea University, Sweden.
SOURCE: VIROLOGY, (1995 Jan 10) 206 (1) 686-9.
Journal code: XEA; 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U10271; GENBANK-U10272
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950307
Last Updated on STN: 19970203
Entered Medline: 19950217

AB Two **adenovirus** isolates from urine, Ad35p (from a bone marrow recipient) and Ad34a (from a hemorrhagic cystitis patient), were compared regarding their fiber gene organization and hemagglutinating capacity. The fiber serves as the **ligand** between the **virus capsid** and the host cell receptor. The Ad35p fiber gene encoded a 323-amino-acid protein, and the Ad34a fiber gene a 325 amino acid protein. The two fibers manifested 62.4% overall amino acid sequence homology, the differences predominantly occurring within the knob region where sequence homology was only 49.5%. The knob region of Ad34a was virtually identical to that of Ad11p which also causes hemorrhagic cystitis. Unlike all other known subgenus B **adenoviruses**, in the Ad35p fiber an asparagine constituted the C-terminus.

Although both Ad34a and Ad35p viruses can hemagglutinate monkey erythrocytes, the hemagglutination inhibition test showed them to differ from each other in the epitopes expressed on the fibers.

L15 ANSWER 27 OF 30 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 94309191 MEDLINE
DOCUMENT NUMBER: 94309191 PubMed ID: 8035520
TITLE: Characterization of the knob domain of the **adenovirus** type 5 fiber protein expressed in Escherichia coli.
AUTHOR: Henry L J; Xia D; Wilke M E; Deisenhofer J; Gerard R D
CORPORATE SOURCE: Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas 75235-8573.
SOURCE: JOURNAL OF VIROLOGY, (1994 Aug) 68 (8) 5239-46.
Journal code: KCV; 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940825
Last Updated on STN: 19970203
Entered Medline: 19940815

AB The **adenovirus** fiber protein is used for attachment of the virus to a specific receptor on the cell surface. Structurally, the protein consists of a long, thin shaft that protrudes from the vertex of the **virus capsid** and terminates in a globular domain termed the knob. To verify that the knob is the domain which interacts with the cellular receptor, we have cloned and expressed the knob from **adenovirus** type 5 together with a single repeat of the shaft in Escherichia coli. The protein was purified by conventional chromatography and functionally characterized for its interaction with the **adenovirus** receptor. The recombinant knob domain bound about 4,700 sites per HeLa cell with an affinity of 3 x 10(9) M-1 and blocked **adenovirus** infection of human cells. Antibodies raised against the knob also blocked virus infection. By gel filtration and X-ray diffraction analysis of protein crystals, the knob was shown to consist of a homotrimer of 21-kDa subunits. The results confirm that the trimeric knob is the **ligand** for attachment to the **adenovirus** receptor.

L15 ANSWER 28 OF 30 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95030510 EMBASE
DOCUMENT NUMBER: 1995030510
TITLE: Mechanism of **adenovirus**-mediated endosome lysis: Role of the intact **adenovirus** capsid

structure.

AUTHOR: Seth P.
CORPORATE SOURCE: Medical Breast Cancer Section, Medicine Branch, Div Cancer Treatment, NCI, NIH,Bethesda, MD 20892, United States

SOURCE: Biochemical and Biophysical Research Communications, (1994) 205/2 (1318-1324).
ISSN: 0006-291X CODEN: BBRCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Adenoviruses** have been previously shown to enhance the delivery of many **ligands** including proteins and plasmid DNAs to the cells. The key biochemical step during this process is the ability of **adenovirus** to disrupt (lyse) the endosome membrane releasing the co-internalized virus and the other **ligands** into the cytosol. To understand the role of the **adenovirus** proteins involved in the endosome lysis, it is further shown here that empty capsids of **adenovirus** also possess this membrane vesicle lytic activity though the activity is about 5-times lower than the **adenovirus**. Incubation of **adenovirus** with low concentration of ionic detergent or brief exposure to 45.degree.C destroyed this lytic activity without affecting the **adenovirus** binding to cell surface receptor, suggesting the lytic activity of **adenovirus** to be of enzymatic nature. However, exposing **adenovirus** to conditions that can disrupt **adenovirus** capsid structure such as heating at 65.degree.C, treating with 0.5% SDS, treating with different proteases, dialyzing against no glycerol buffer, treating with 6 M urea or with 10% pyridine, and sonication destroyed the **adenovirus**-associated lytic activity. Results suggest the requirement of an intact capsid structure for **adenovirus**-mediated lysis of the endosome.

ACCESSION NUMBER: 93192854 EMBASE
DOCUMENT NUMBER: 1993192854
TITLE: Hemagglutination properties and nucleotide sequence analysis of the fiber gene of **adenovirus** genome types 11p and 11a.
AUTHOR: Mei Y.-F.; Wadell G.
CORPORATE SOURCE: Department of Virology, University of Umea,S-901 85 Umea, Sweden
SOURCE: Virology, (1993) 194/2 (453-462).

Tuberculosis
016 Cancer
022 Human Genetics
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English

AB Gene therapy, a revolutionary therapeutic modality, is currently being tested in oncology patients but may ultimately permeate all medical disciplines before the end of this decade.

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